

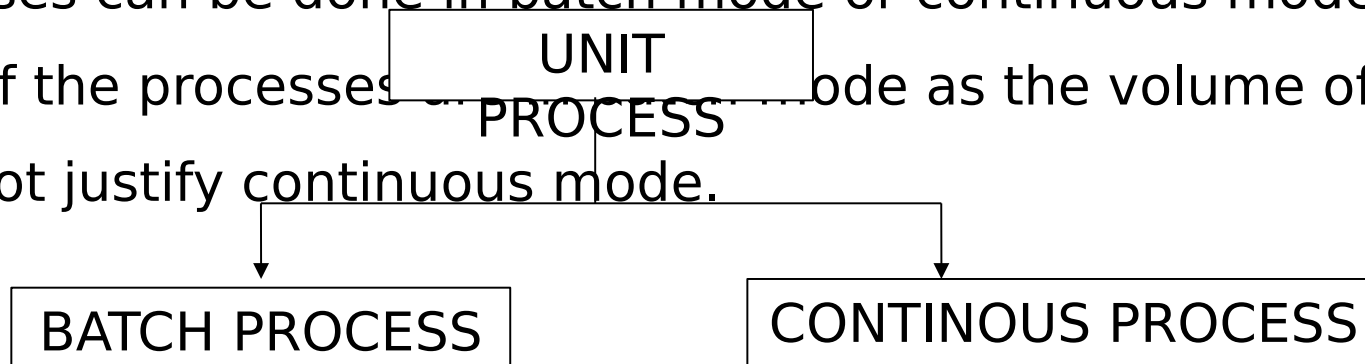


- **Learning Objectives:**
 - On completion of this course. The trainee will
 - Define and differentiate Unit Process and Unit Operation
 - Types of Unit Processes and Unit operations
 - Explain the components of the equipment and the manufacturing procedure
 - Explain Equipment care to be taken on day to day basis.
 - Explain the problems and troubleshooting of various unit operations.
- **Target Audience:** Up to Jr. Manager of PRD, Process Engineering
- **Expected Outcome**
 - Speedy closure of Issues incident Reduction, Improved yield & Quality consistency

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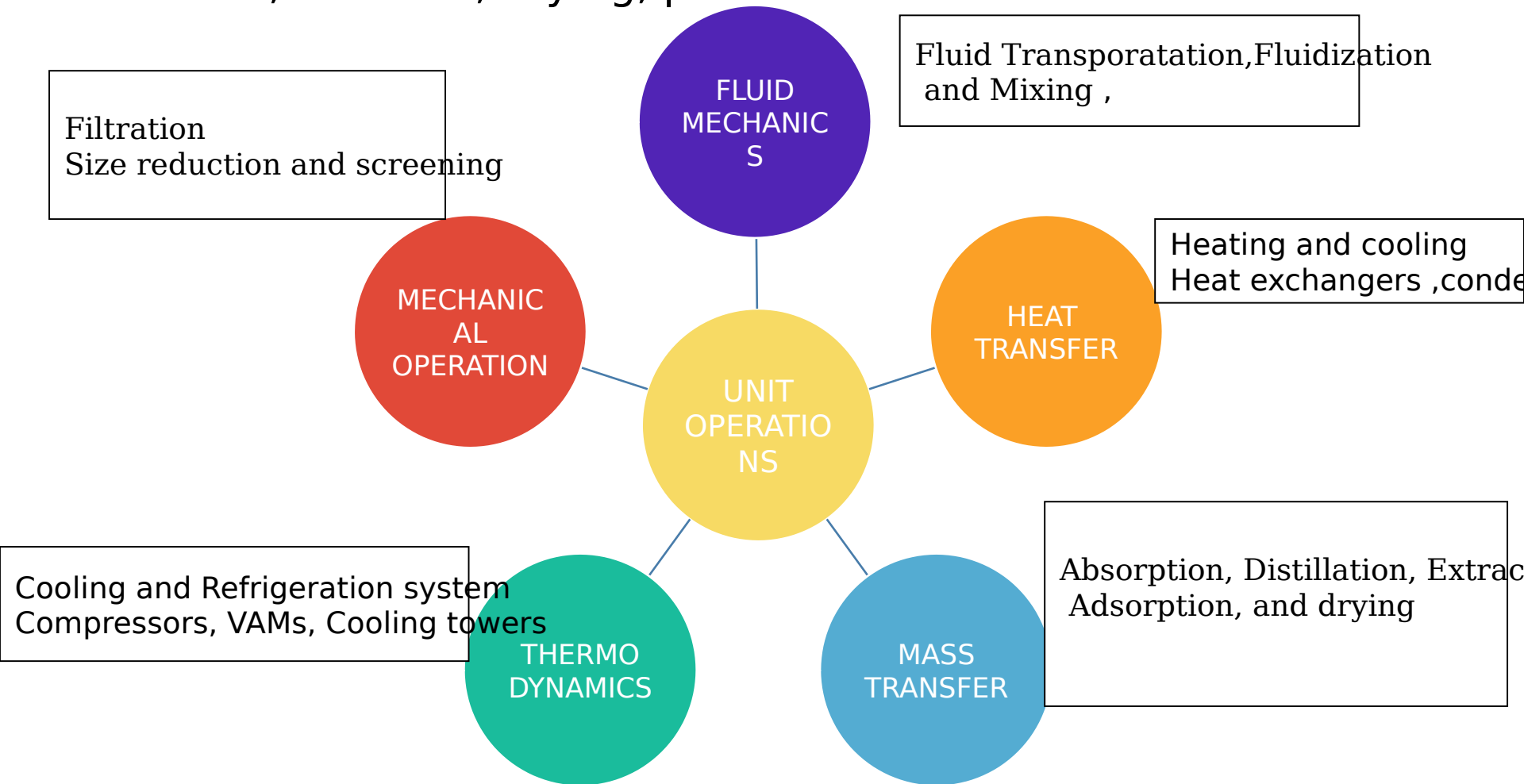
- Unit Process
- Unit Operation
- Typical Manufacturing steps
- Reactor Classification and its accessories equipment
- Reaction, Extraction & Work-Up
- Distillation and Evaporation
- Crystallization, Product Isolation and drying
- Powder processing
- Packing
- Plant Utilities

- Processes that involve chemical reaction to get desired or required chemical molecules. A chemical reaction involves a chemical change.
- Generally API industries deal with organic compounds.
- Eg: Condensation, esterification, hydrogenation (Reduction) etc.
- Processes can be done in batch mode or continuous mode. In MSN most of the processes are done in batch mode as the volume of products does not justify continuous mode.



UNIT OPERATION

- Unit operation is a basic step in a process and it involves a physical change such as separation, crystallization, distillation, evaporation, extraction, filtration, drying, particle size reduction etc.



Typical Manufacturing steps

Reaction

2 or more Key starting materials are reacted in

Extraction

Desired product is take by using suitable solvent based on solubility

Work-up

Impurities are removed by extractions / washings



Reactor

Distillation

Solvents are distilled / chased with different solvents to remove selective impurities or improving isolation

Filtration

Product isolated by filtration separating liquid and get wet cake



Centrifuge

Drying

Wet cake or material is dried to reduce solvents or water content .

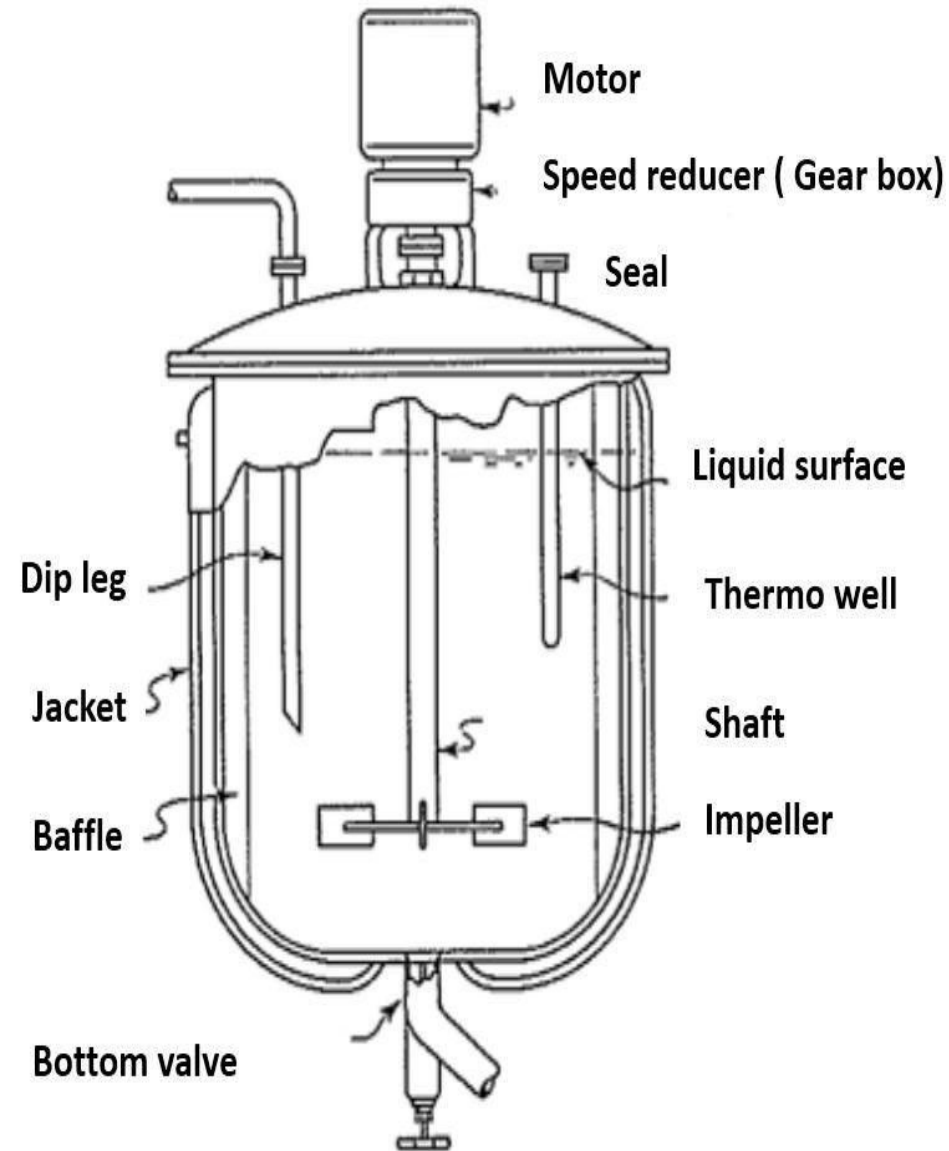
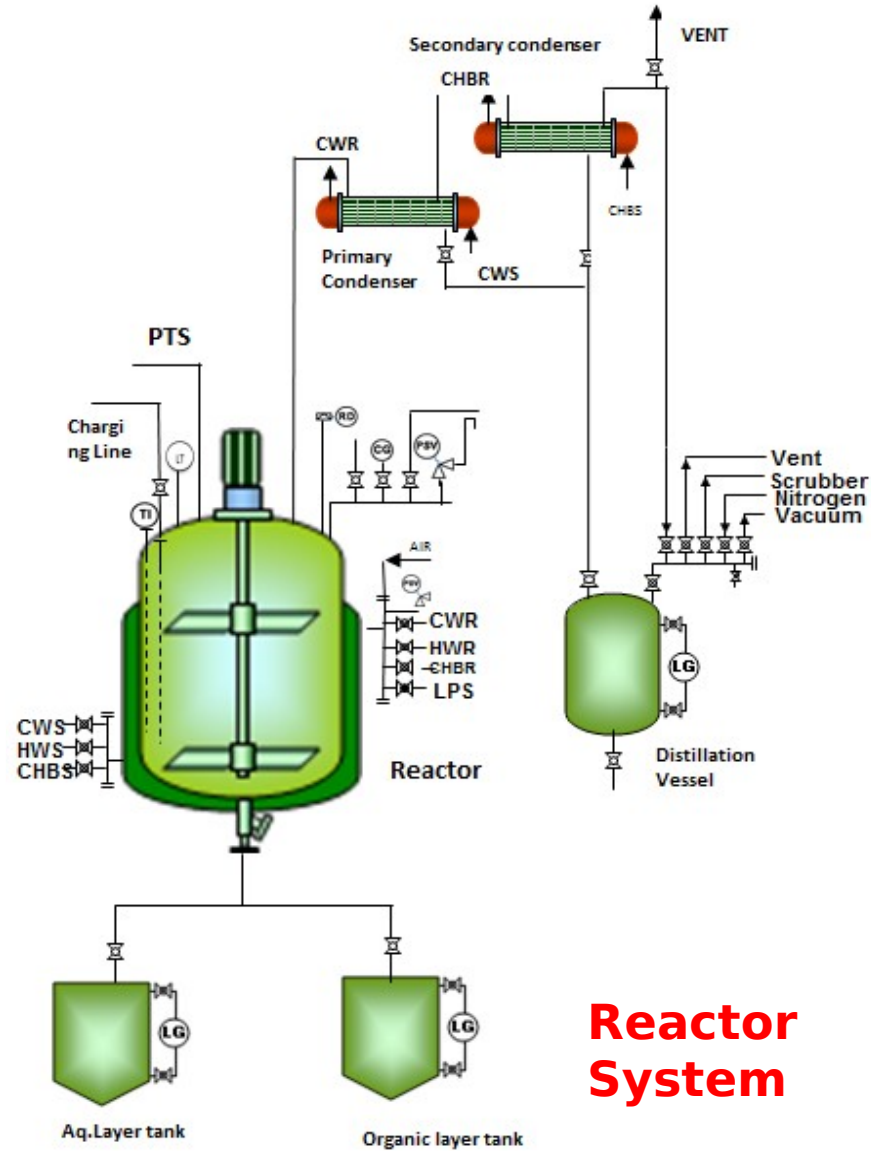


ANFD

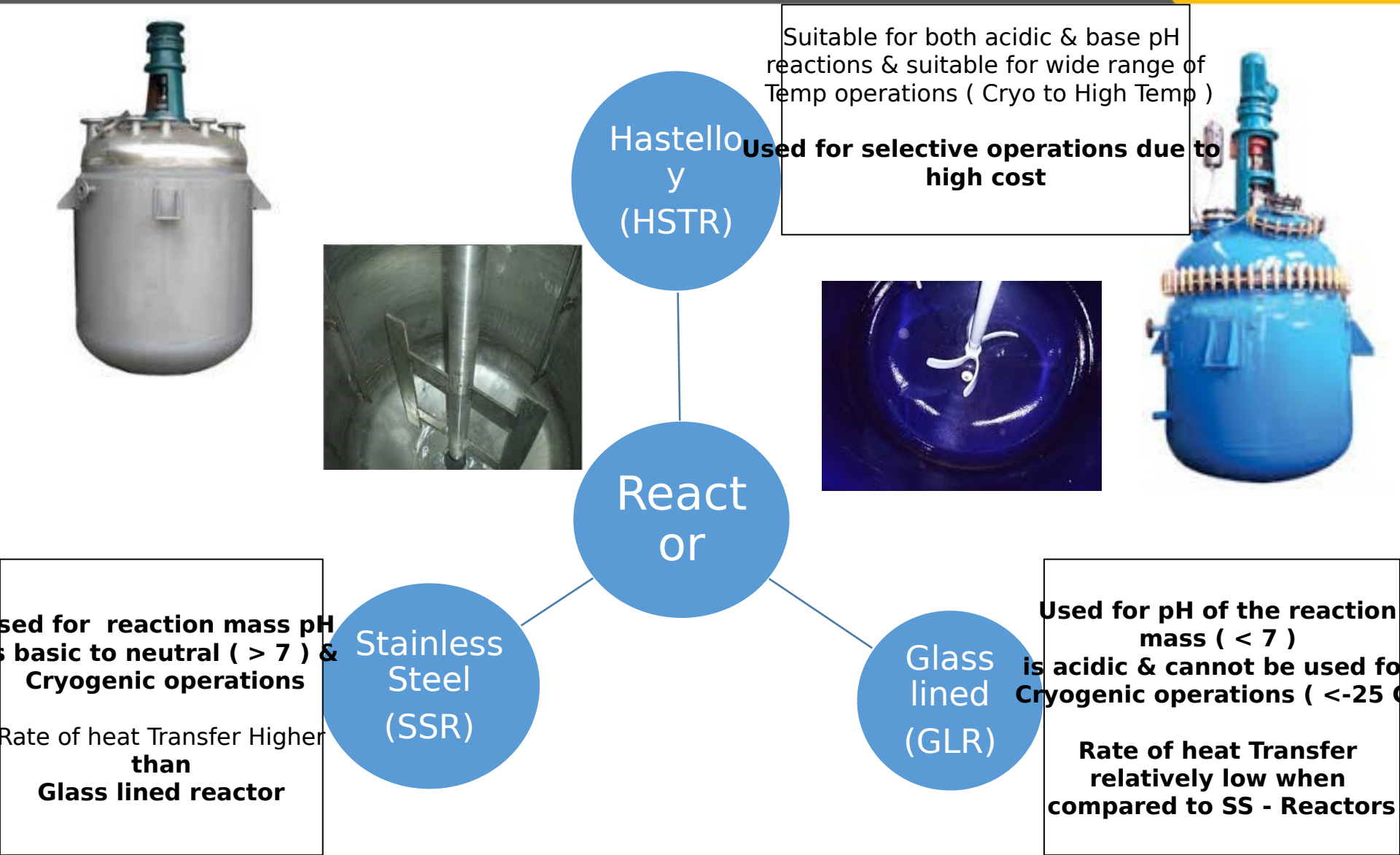
Powder processing

Dried material is processed to achieve PSD and packed as per requirement

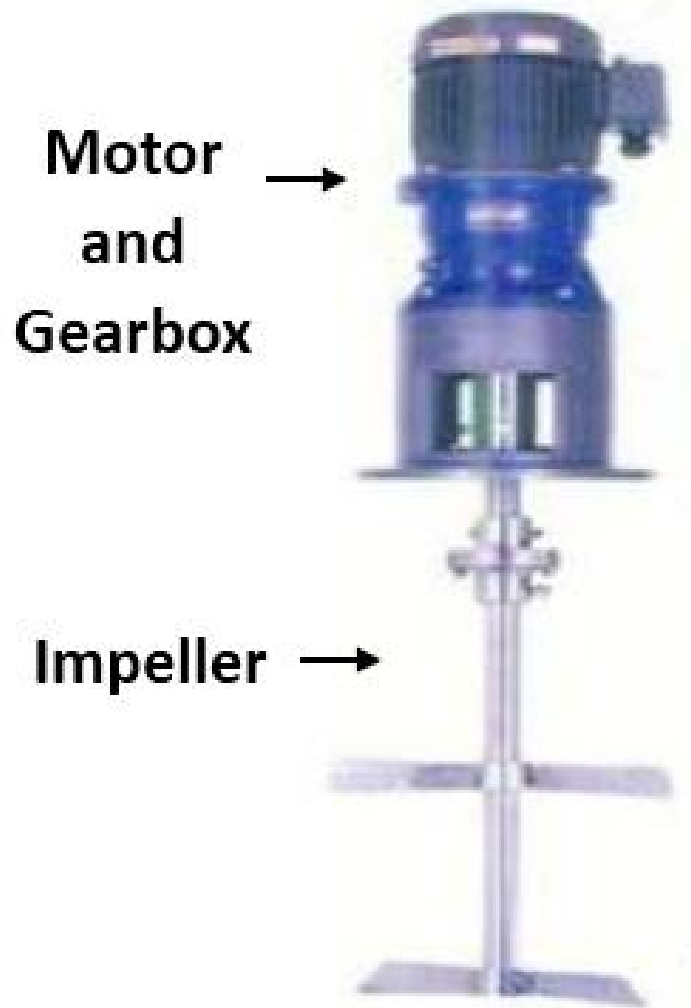
Schematic of a Typical Batch reactor set-up



Reactor Classification Based on MOC



MOTOR AND GEAR BOX SETUP



AGITATOR



Reduction ratio of gear =
$$\frac{\text{Output RPM of gear}}{\text{Input RPM to gear}}$$

1. What is reactor system?
 - Reactor, condenser, charge tank, vapour line, collection tank
2. What is unit process? Give an example
 - That involves chemical reaction. Ex: Hydrogenation
3. What are the types of Unit Process
 - Batch and Continues
4. What is unit operation?
 - that involves physical process. extraction, separation, crystallization, distillation
5. What are the typical manufacturing steps
 - Reaction, Extraction, work-up, Distillation, Filtration, Drying, Powder processing
6. Which MOC of reactor is used for $\text{pH} > 7$ and $\text{pH} < 7$?
SSR and GLR
5. What is reduction ratio of gear?
 - Output RPM of gear / input RPM to gear

Type of impeller and speed of agitation is important in mixing.

Why is mixing important ?

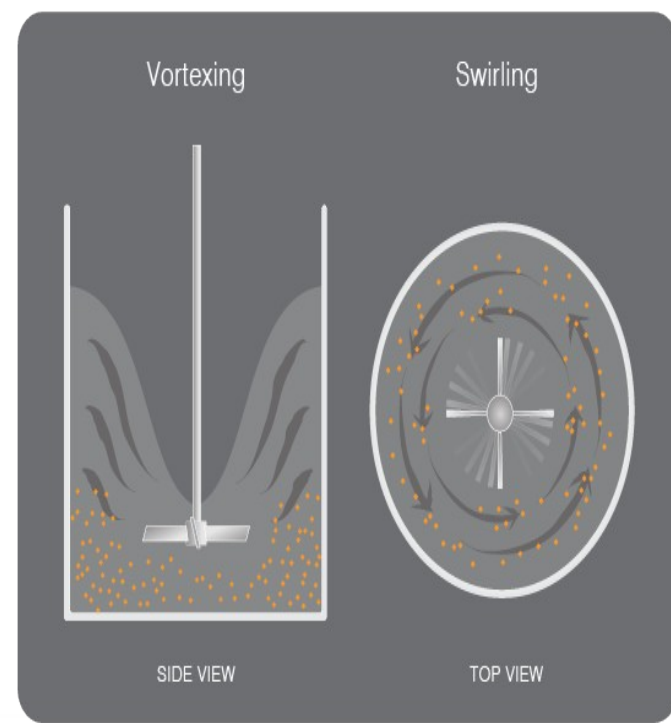
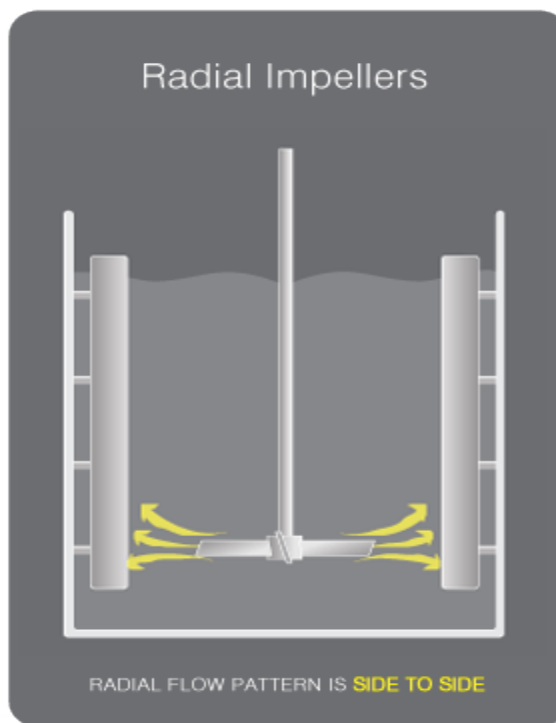
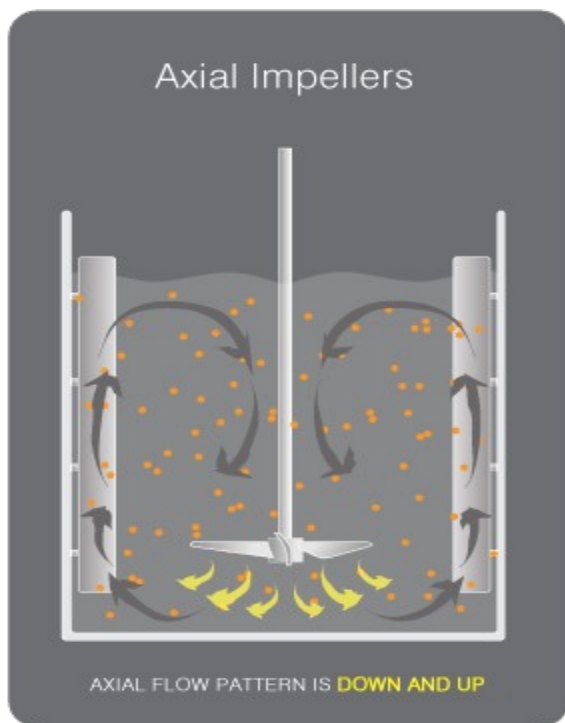
1. Dissolution of an intermediate in a stirred vessel prior to reaction (mass transfer)
2. Precipitation of API or intermediate (crystallization)
3. Minimization of impurity formation during reaction (parallel/consecutive homogeneous reactions call for intense mixing)
4. Suspension of a catalyst during heterogeneous catalysis (mass transfer + heterogeneous reaction – solid/liquid/gas)
5. Preparation of Nano/Micro-particles or droplets of desired particle size distribution (particle size control/reaction)
6. Achievement of uniform temperature in a crystallizer and temperature control (heat transfer) – to avoid material degradation/ surface pre-mature crystallization

Agitator

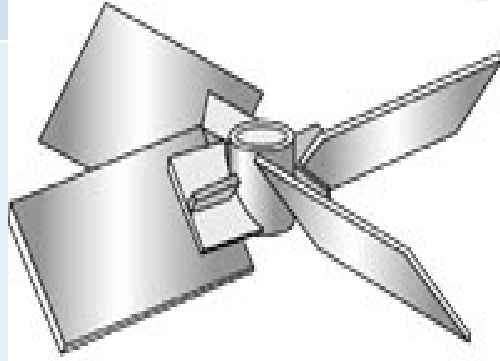
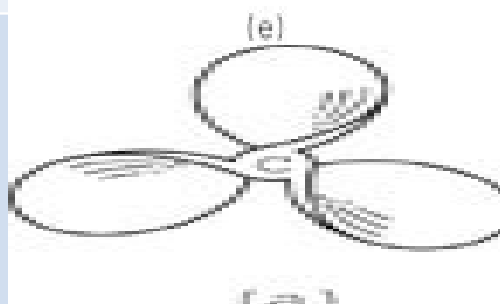
Once the purpose of agitation is finalized, the type of impeller is selected to achieve the desired flow pattern and flow regime.

Types of flow patterns:

- **Axial Mixing**-The most common flow patterns in mixing are axial (down and up)
- **Radial Mixing**-side to side
- **Tangential Mixing**-The flow pattern seen when tangential or rotational flow dominates is a swirling of the reactor contents, often with a surface vortex



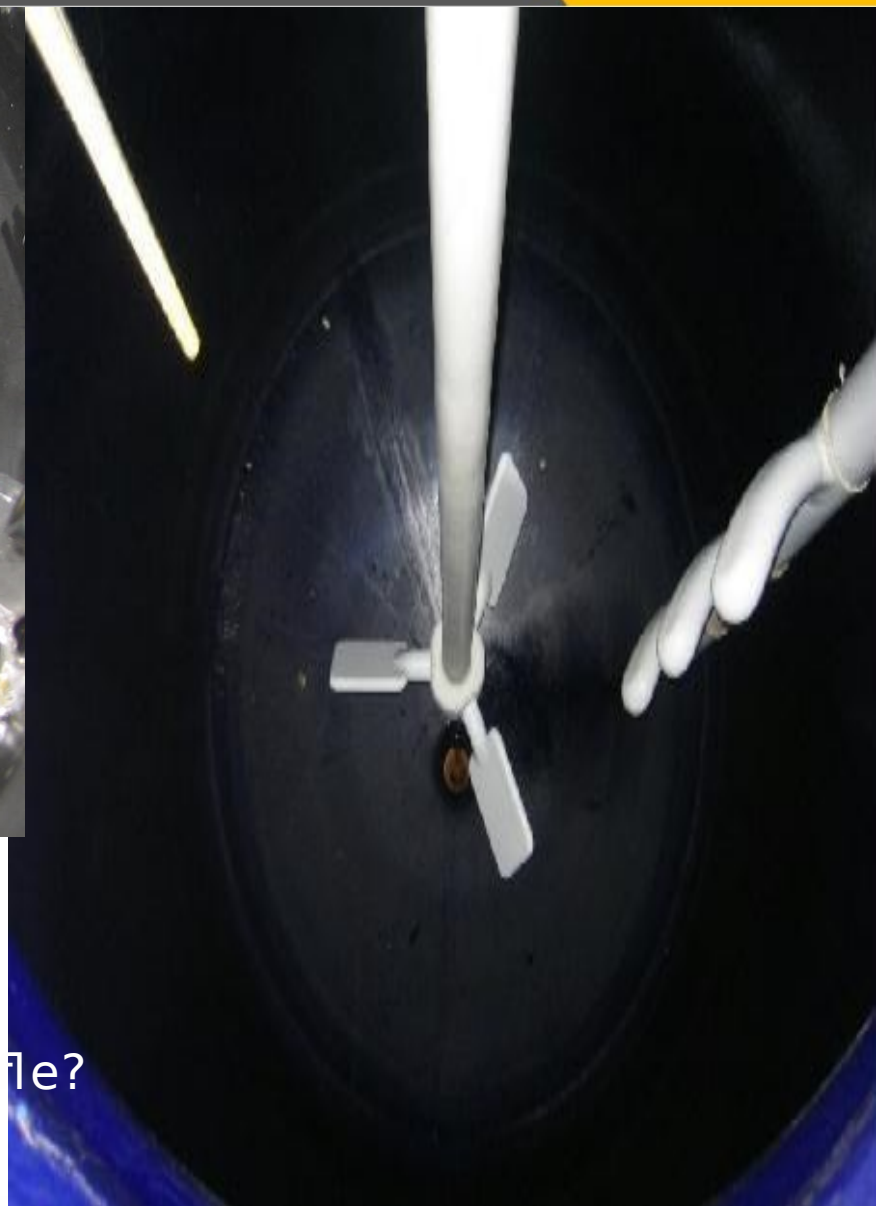
AGITATOR TYPES

Flow pattern	Types of Agitators	Usage	Photos/image
Radial flow	Retreat curve impeller	General/multiple purpose mixing suitable for low to medium viscosity mixing	
Axial flow	Pitch blade Turbine	It will be suitable for blending suspension and heat transfer and not suitable for dispersion mass	
Axial flow	Marine propeller	Suitable for mixing low viscosity liquids	

AGITATOR - TYPES

Flow pattern	Types of Agitators	Usage	Photos/ image
Tangential	Anchor	Tangential flow, high shearing rate at edges, minimum deposits on the vessel wall. Low speeds. High viscous/ slurries /crystallization	
Radial	Flat blade/ Pitch disc Turbine	Gas liquid dispersion (Hydrogenation)	
Radial	Paddle type	Ideal for applications where agitation close to the bottom of the tank is desired. Suitable for suspension mass mixing	

BAFFLES IN REACTOR



le?

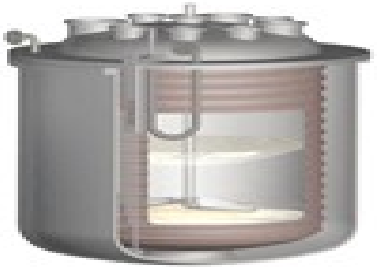
Advantages:

- Baffles are typically introduced to prevent vortex formation and convert tangential (rotational) flow into axial (vertical) flow
- Baffles are used to generate turbulent flow system important for effective mixing

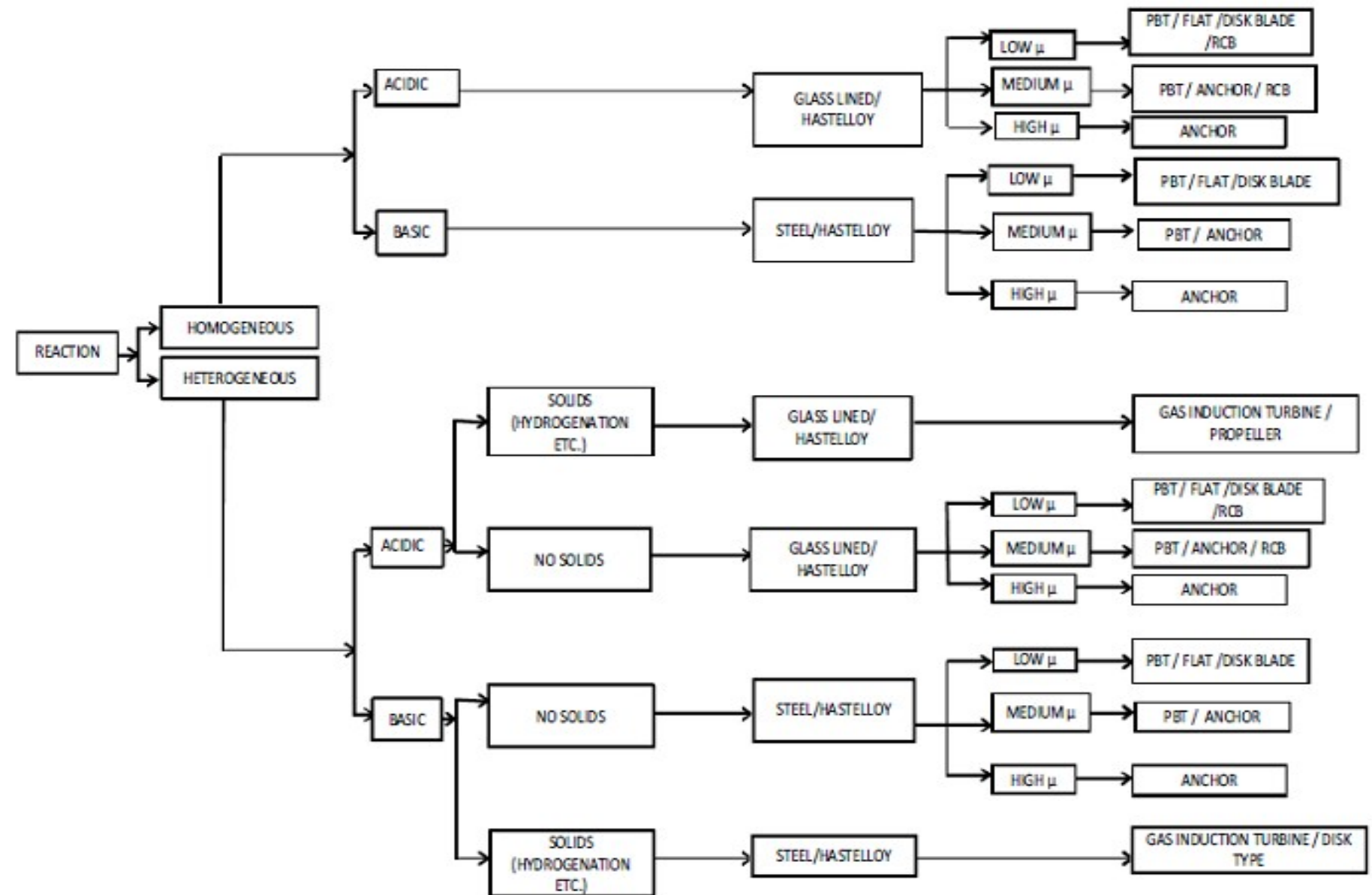
Challenges

- Gap between the baffles and the wall leads to accumulation of material (e.g., solids) it will take time in cleaning and can lead to cross contamination if not properly cleaned.
- Baffles produce efficient mixing and can affect the crystallization and form change. We may have to remove baffles in such cases
- Increased power consumption.

HEATING & COOLING JACKET TYPES

JACKET TYPE	USAGE	PHOTOS
Single external jacket	Conventional jacket, is generally very inefficient for heat transfer because the flow media has an extremely low velocity resulting in a low heat transfer coefficient	 
Half coil jacket or limpet coil jacket	In half coil jacket type will not have dead pockets of condensate and will have better heat transfer compare to Single external jacket	
Internal coil	Liquid nitrogen is circulated through internal coils of a reactor. This is used where large heat transfer rates (rapid cooling) is required.	
Double Jacket	Double jacket system will be used to apply heating medium and cooling medium separately	

REACTOR & AGITATOR SELECTION CHART



UTILITIES FOR HEATING AND COOLING



Utilities	Temperature range
Heating utilities	
Low pressure saturated steam(<3.0 kg/cm ²)	95 - 144°C
High pressure saturated steam(3.0 - 8.0 kg/cm ²)	144 - 180 °C
Hot water	35 - 95 °C
Therminol /Dowtherm(Single fluid utility)	180 - 200 °C
Cooling utilities	
Cooling tower water	High temp to 35 °C
Chilled water	8 to 35 °C
Chilled brine	-35 to 8 °C
Liquid nitrogen (Dedicated jacket utility)	-100 to - 35 °C
Therminol/Dowtherm(Single fluid utility)	-100 to 180 °C

Follow the principles of progressive heating or cooling.

Follow jacket cleaning schedule for better heat transfer and ensure no mix ups

Seals :

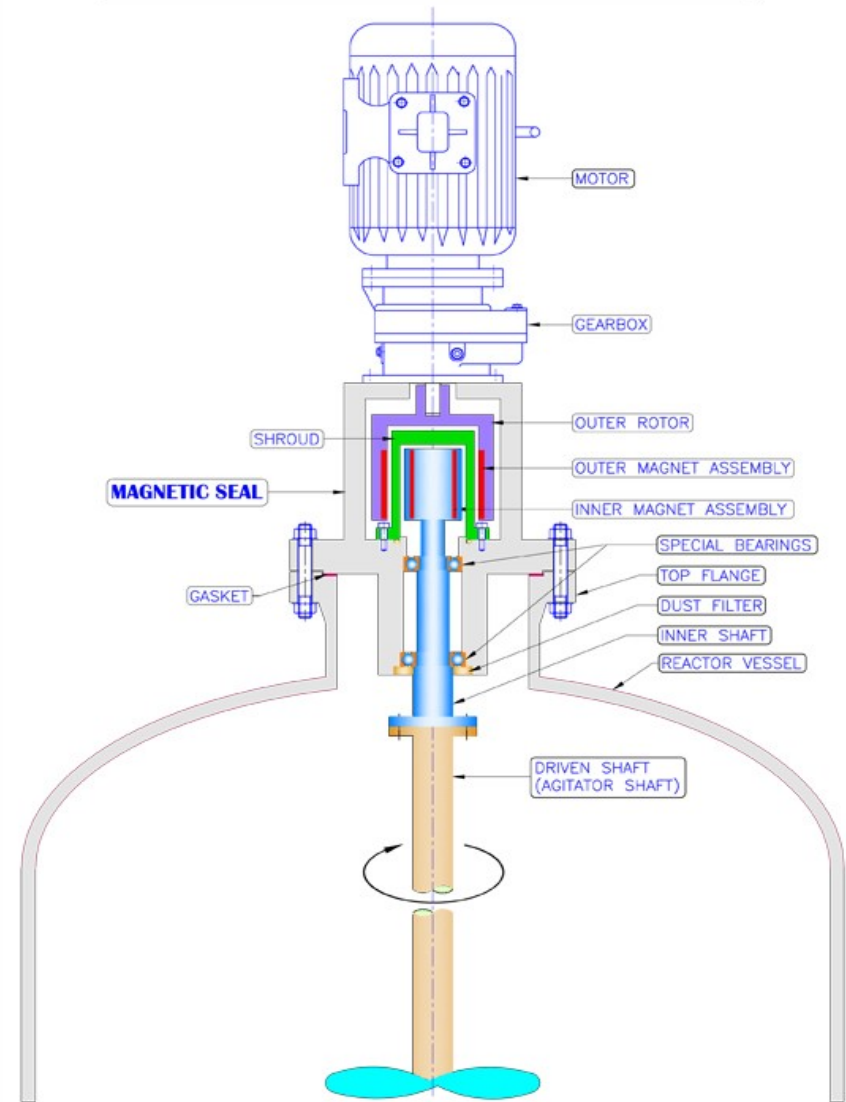
Seal prevents the contents of the reactor from escaping during operation, which could cause harm to the environment, the equipment (may affect motor) the material inside the equipment, and any personnel in the vicinity.

Gland packing

Mechanical seal

- Wet seals
- Dry seals
- High purity seals
- Magnetic seals - hydrogenator

MAGNETIC DRIVE ASSEMBLY



1. Why mixing is important?
 - Dissolution and precipitation of API's, Suspension of catalyst, Achievement of uniform temperature in the reactor.
2. What are types of agitators and their respective flow patterns?
 - Flat blade turbine, Paddle type, anchor, PBT
 - radial Flow pattern, Axial flow pattern tangential flow pattern
2. What are the disadvantages of baffles?
 - Cleaning, power consumption, crystallisation can get affected.
3. What is progressive cooling? cool mass from 80 deg to 2 deg C
 - Tower water, chilled water, brine
4. Which coil/ jacket provides the most efficient heat exchange?
 - Internal coil □ external limpet coil □ Simple jacket
5. Why are there seal on reactor agitators?
 - Seal prevents the contents of the reactor from escaping during operation, which could cause harm to the environment, the equipment

Measurements on Reactor

- Temperature
- Pressure
- Flow
- Level (gauge rod)
- Weight



Temp. RTD sensors



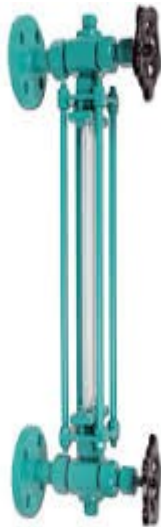
Temp. Digital RTD sensors



mechanical flow meter



Digital flow meter



Level Indicator



Level Transmitter

Selection of Temperature sensor



1. When to use Top temperature sensor?
2. When to use bottom temperature sensor?
3. Is there any specific installation requirement for bottom sensor?
4. Is bottom temperature sensor suitable for all types of reaction mass?
5. Why an oil is used to fill the thermo well?
6. Are there different grades of oil to be filled in thermowell?
7. How do we measure temperature in transfer line or distillate line without thermo well?

TEMPERATURE SENSORS

S.No	Type of Contact	Type of Temperature sensor	Usage	Photos
1	Direct contact	Top sensor	It is more reliable and practical to use one location over the other when monitoring and controlling the temperature in a chemical process	 RTD sensor
2	Direct contact	Bottom sensor	Used for measuring temperature at minimum level volume . If it is measure for slurry then temperature won't be correct	
3	Non contact	Infrared sensor (Portable Instrument)	Used for measuring temperature at utility lines and transfer lines	

PRESSURE GAUGES

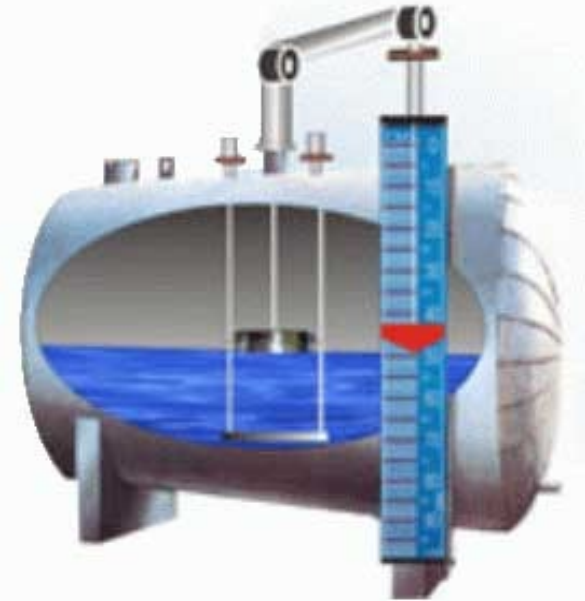
S.No	Type of Gauge	Usage	Photos
1	Pressure Gauge	For measuring of positive pressure (air pressure, steam, nitrogen ,utilities etc.) Why does pressure gauge display ~ 700mm at Hyd instead of 760mm?	
2	Vacuum Gauge	Used for measuring Negative pressure. (Vacuum pumps)	
3	Compound Gauge	Used for measuring of both Positive pressure and negative pressure (reactor)	
4	Transmitter s	Used for auto data recording and control	

FLOW METER

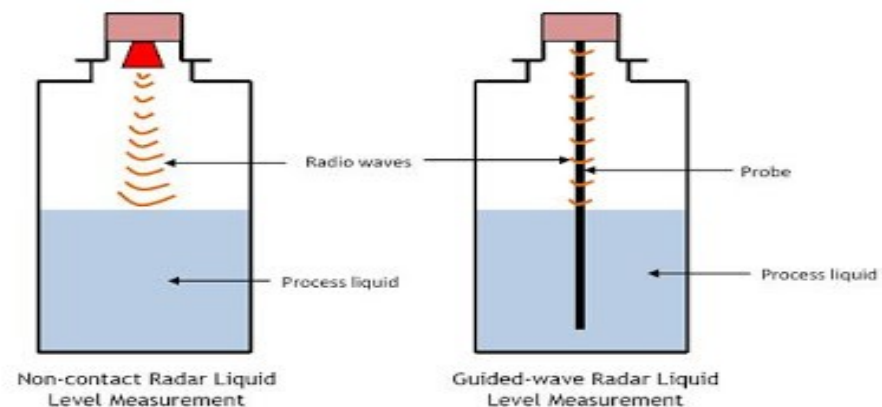
Sr. No	Type of Flow instruments	Usage	Photos
1	Flow meter	For measuring of flow online (Solvent charging/water charging in reactor). Installed in Horizontal position only	
2	Rota meter	For measuring of liquid flow in line (Solvent charging in reactor ,) Installed in vertical position only For measuring of gas flow in line (Nitrogen flow in reactor/centrifuge) Installed in vertical position only. Temp and Sp. gravity range should be as per rotameter spec	 

LEVEL MEASUREMENT

- Level measurement of the reactor is critical and it will have impact on distillation concentration, crystallization and which in turn will affect the quality of the product
- Types of Level measurements in reactors and Receivers
- **Direct measurement & without contact** (periodic calibration important. Periodicity depends on criticality of operation)
- LEVEL TRANSMITTER
- LEVEL RADAR
- **Indirect measurement & with contact**
- GAUGE ROD
- CALIBRATED GLASS TUBE IN RECEIVER
- FLOAT IN RECEIVER.

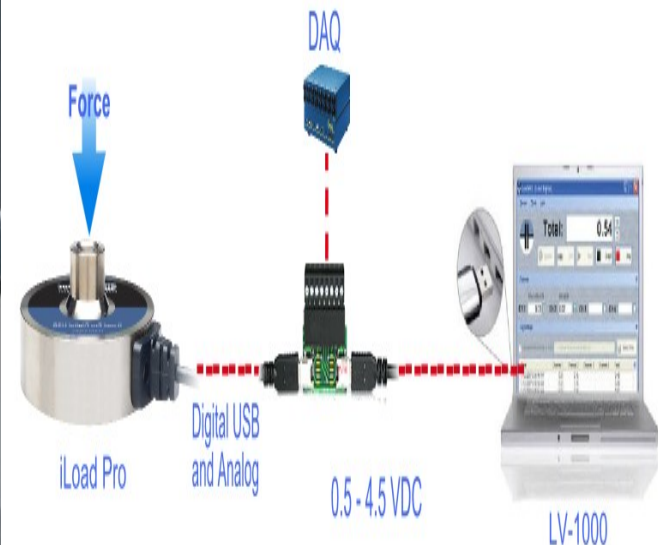


Level Indicator



LOAD CELL

- A load cell is a sensor or a transducer that converts a load or force acting on it into an electronic signal.
- This electronic signal can be a voltage change, current change or frequency change depending on the type of load cell and circuitry used.
- There are many different kinds of load cells.
- **Maintenance and errors. Types of load cells in MSN?**



pH meters

Principle:

When immersed into the process solution, the measuring electrode produces an electrical signal proportional to the hydrogen ion activity. The reference electrode provides a stable basis for comparison and completes the circuit. These two electrodes constitute an electrolytic cell with a millivolt output that is proportional to the pH of the solution.

Purpose:

To know completion of reaction and also for isolation of impurities. This also includes selective transfer of product from one layer to another. Therefore pH is adjusted before layer separation.



1. What are measurement on Reactor?
 - Temperature
 - Pressure
 - Flow
 - Level (gauge rod)
 - Weight
 - pH
2. What are the main types of temperature sensors?
 - Direct temperature and Indirect temperature
3. what are the types of Level measurements in reactors and Receivers
 - Direct -LEVEL TRANSMITTER,LEVEL RADAR
 - Indirect- GAUGE ROD,CALIBRATED GLASS TUBE IN RECEIVER,FLOAT IN RECEIVER
4. Type of pH meter-
 - Bench top
 - Online
5. What is the purpose and principles of pH meter's?
 - To know completion of reaction and also for isolation of impurities. This also includes selective transfer of product from one layer to another. Therefore pH is adjusted before layer separation.

Process control is by manual and automated

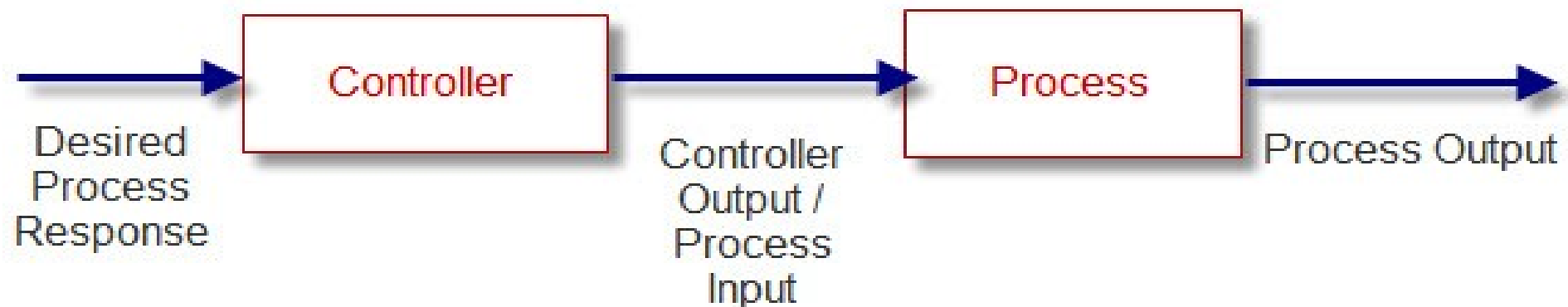
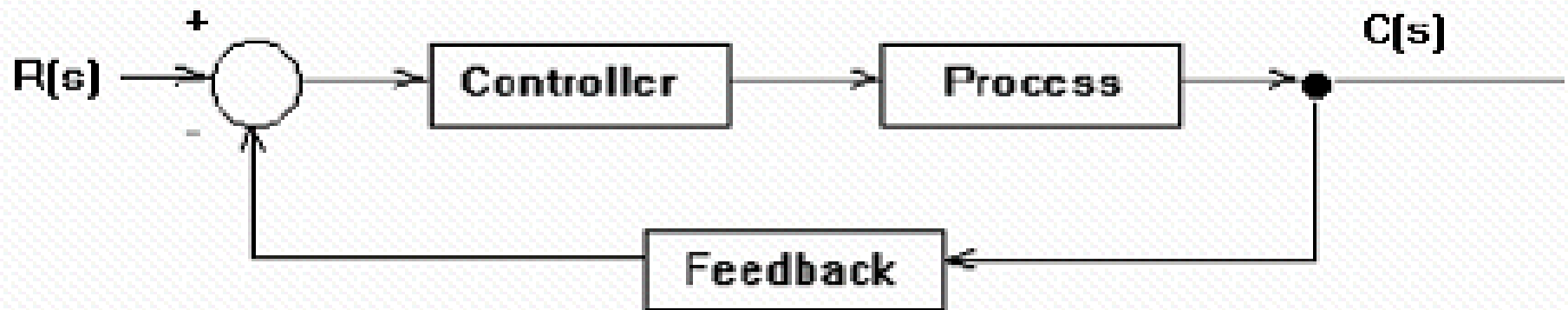
Manual methods – Valve operation, Weighing ,Start and stop of motors, etc.

Automated methods

- The function of a control is to control flow ,level, pressure, pH, composition, etc.
- Depending on the application they are known as PCV, TCV, FCV , mixing valves, ratio control , etc.
- They can be used for on/off control or continuous control – ball valves are not good for continuous control.

Process control involves two type of controls

- o Closed loop control
- o Open loop control



SCADA-DCS DATA LOGGER



- Stands for Supervisory Control And Data Acquisition
- SCADA systems are open loop. It can acquire, log data and alert the operator when the set points are reached
- Where the controls are built in then it is called PLC and it works on close loop control
- Applications of SCADA
 1. Data acquisition
 2. Historical trends
 3. Alarms
 4. Archiving of data

Safety Relief Valve (SRV)

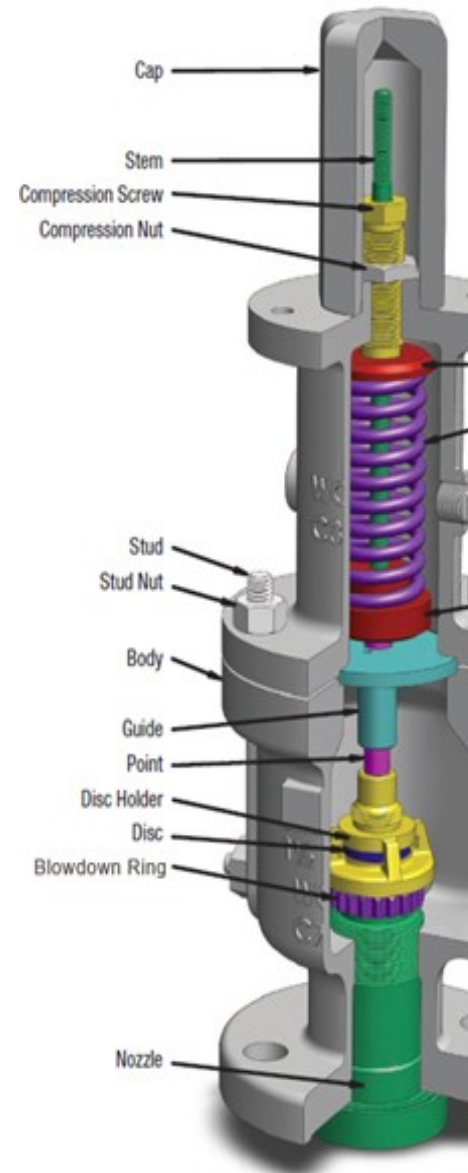
- **SRV is designed for process safety**
- **Set pressure based on operating pressure**

Advantages of SRV:

- Safety Relief Valves are designed to meet specific requirements of Pressure. Variations are possible as these valves are custom engineered to suit the application. Unlike Rupture disc, it is re-usable after pressure relief.

Limitations of SRV:

- Sensitive to the effect on the back pressure (hence pressure accumulation in the protected equipment)
- Chattering can occur in these relief valves due to high built up backpressure values generated by higher pressure loss in the relief valve discharge line.
- High cost of maintenance due to periodic check-up, unlike rupture disc.



Rupture Disc

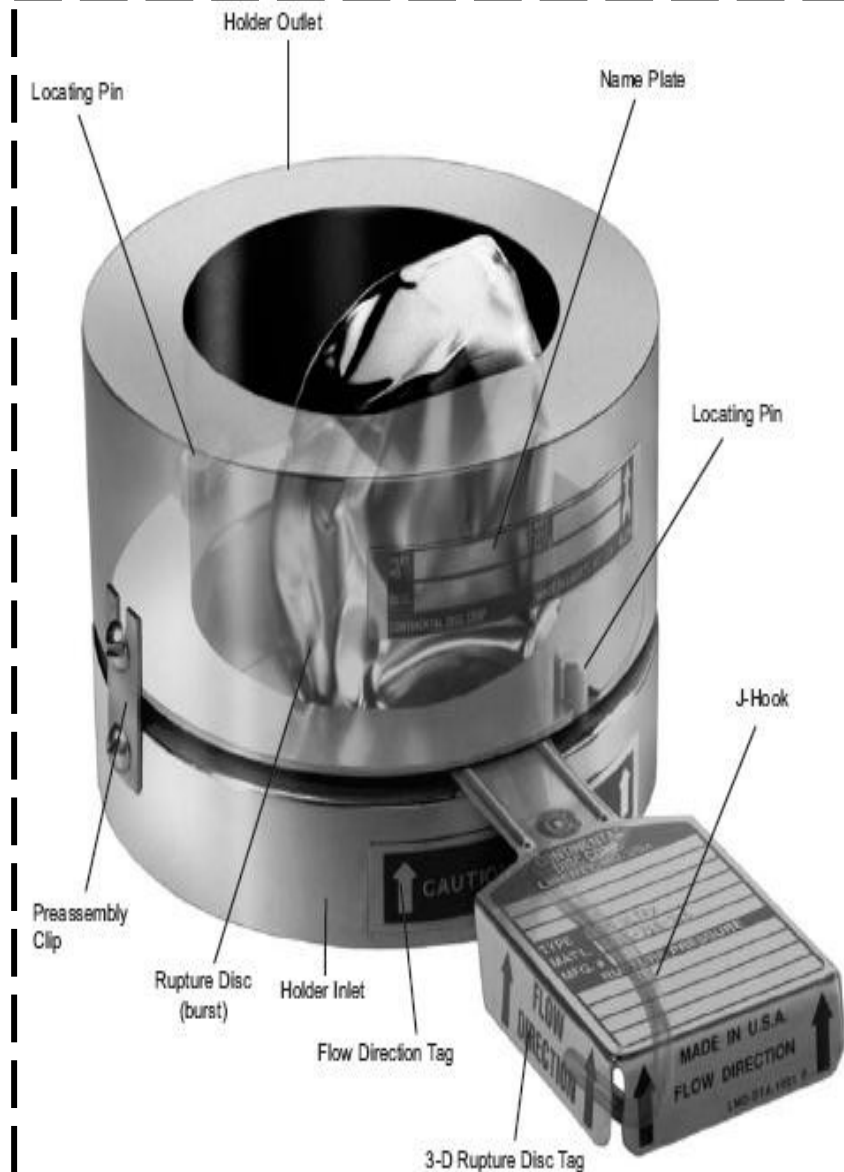
- **Rupture disc is designed for Equipment safety.**
- **Set Pressure based on Equipment operating pressure.**

Advantages of Rupture disc:

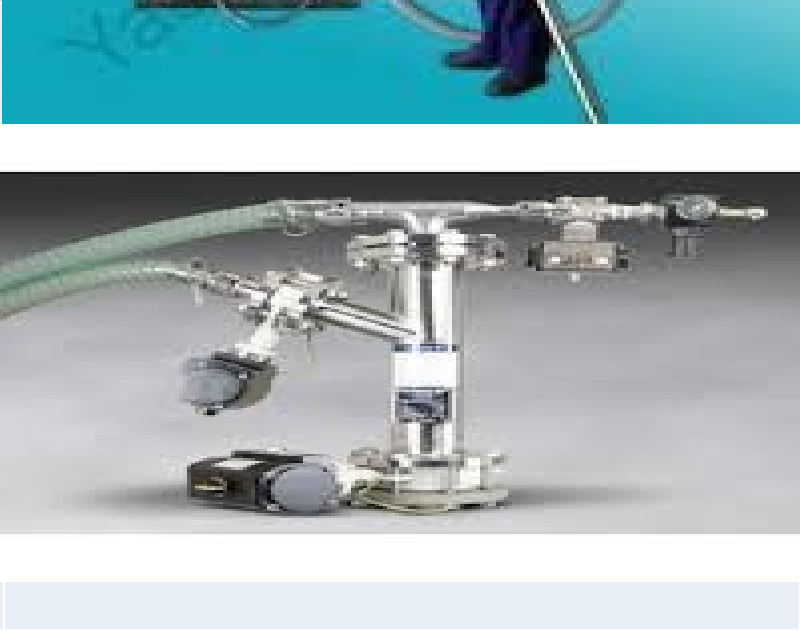
- Suitable in cases where rapid pressure build-up takes place and instantaneous relief is requirement.
- Low cost of maintenance than SRV

Limitations of rupture disc:

- It is irreversible damage. The downtime is incurred to replace the disc (which may result in loss of manufacturing capacity) and cost of replacement (material, labour) also adds up to total cost



MATERIAL CHARGING IN REACTOR

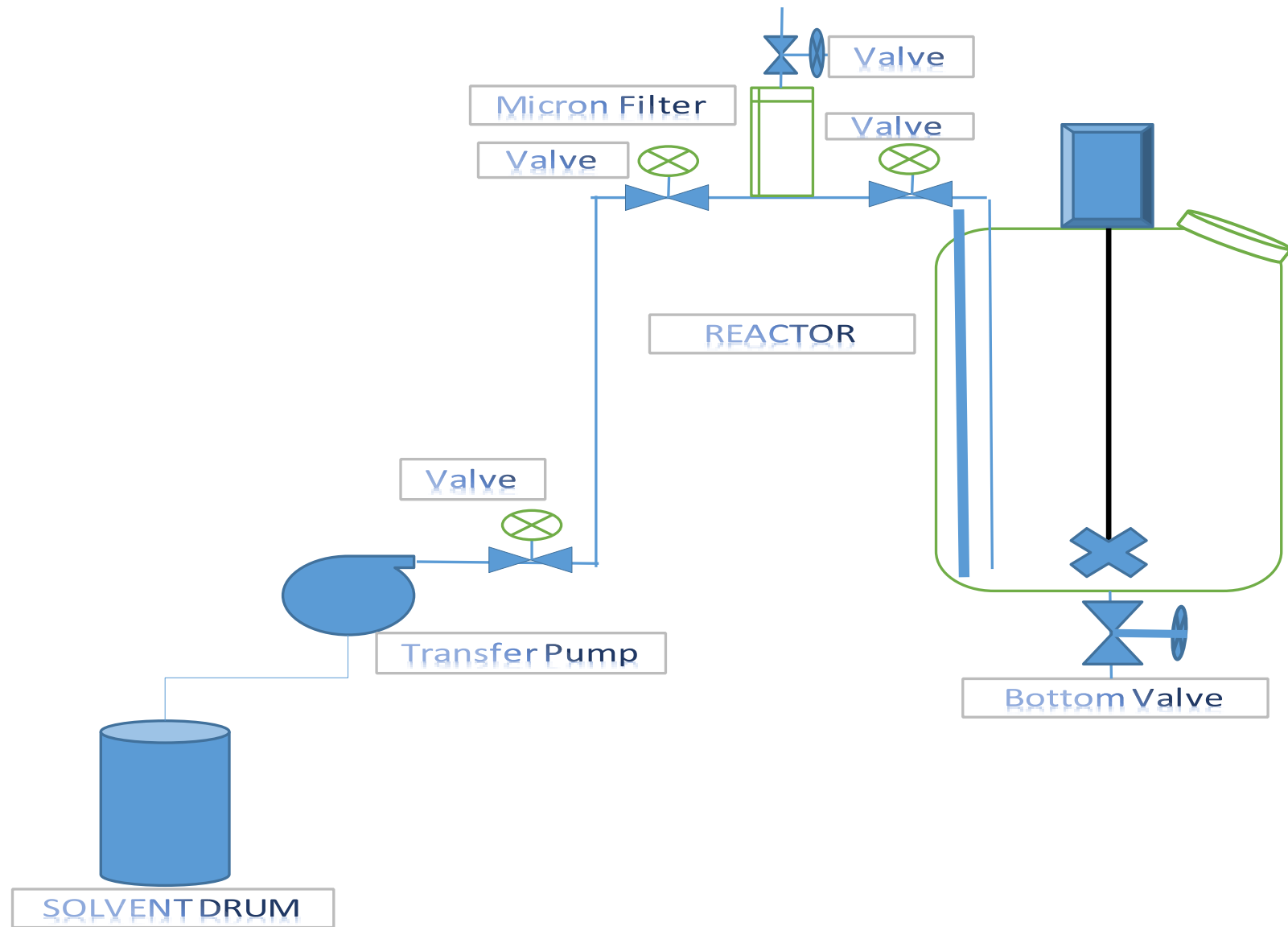
Sr. No	Charging material	Photos
1	Solid is charge by using PTS (powder transfer system) or by manually using scoop if use PTS is more effective and reliable method of transferring and dispensing both dry and wet powders. If using manually by scoop there may chances to spillage, dusting leading to environment hazard.	
2	Liquid is charged by pumps, vacuum, AOD and by Nitrogen pressure in to reactor through dip pipes or J bent provide contained feeding of corrosive and hazardous chemical either above the surface or below the surface to prevent static discharge. Also, in case of adding reagent into a region of high turbulence, such as tip of the agitator blade, dip pipe is useful.	

Precaution for Liquid Charging



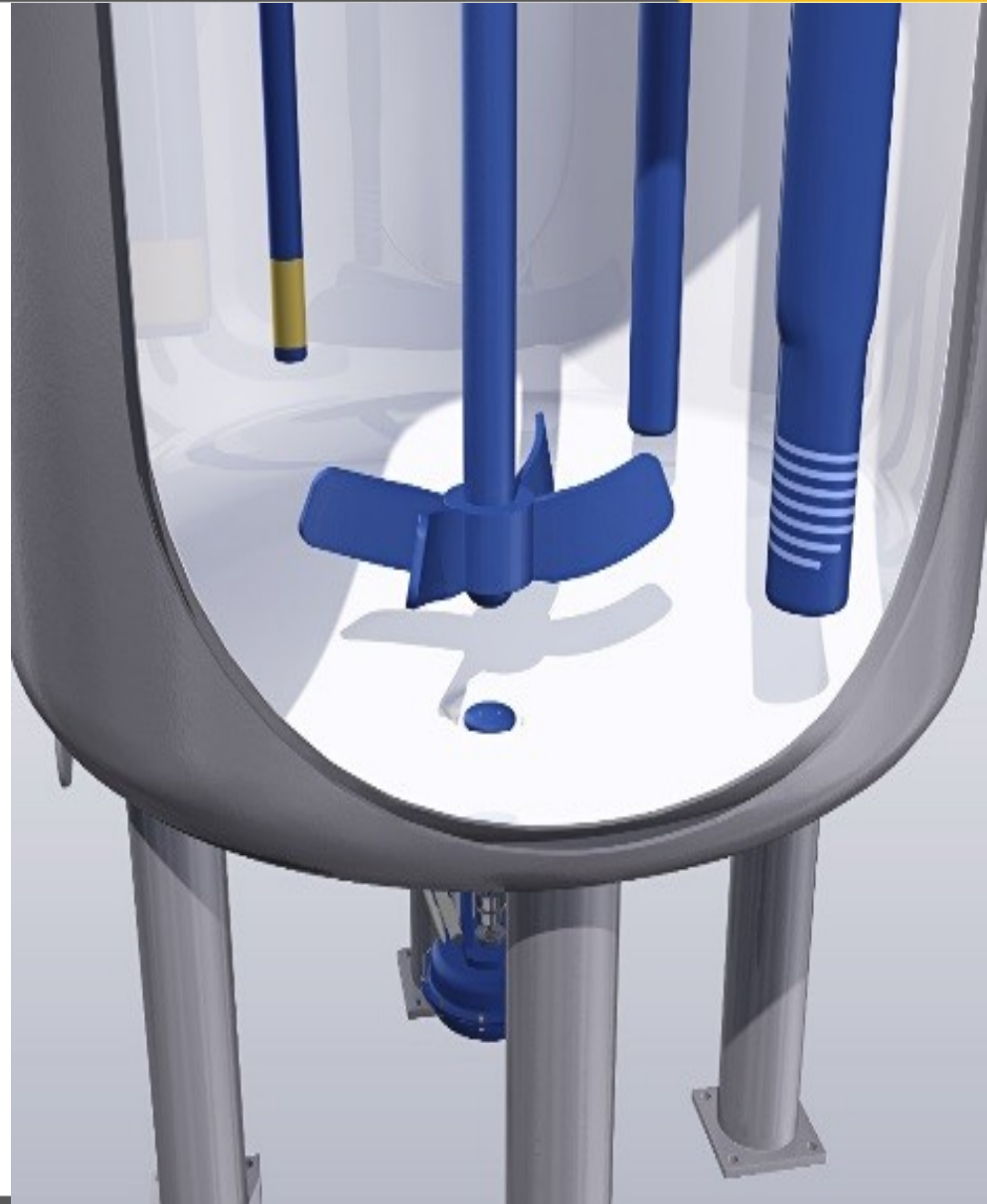
- Liquid charging by AOD and Transfer pump from tank or drums.
- Check the solvent colour and any foreign material.
- Check the solvent if any moisture is available on surface of the solvent.
- Solvent should be charge through micron filter only.
- After charging solvent send the sample for moisture if applicable.
- Use dedicated AOD, transfer pump for charging of solvent.
- Exact solvent quantity to be charge

TRANSFERRING SYSTEM



Chemical Reaction

- A Chemical reaction is process in which one or more substances, the reactants, are converted to one or more different substances, the products. Substances are either chemical elements or compounds. A chemical reaction rearranges the constituent atoms of the reactants to create different substances a



Precaution for Solid Charging

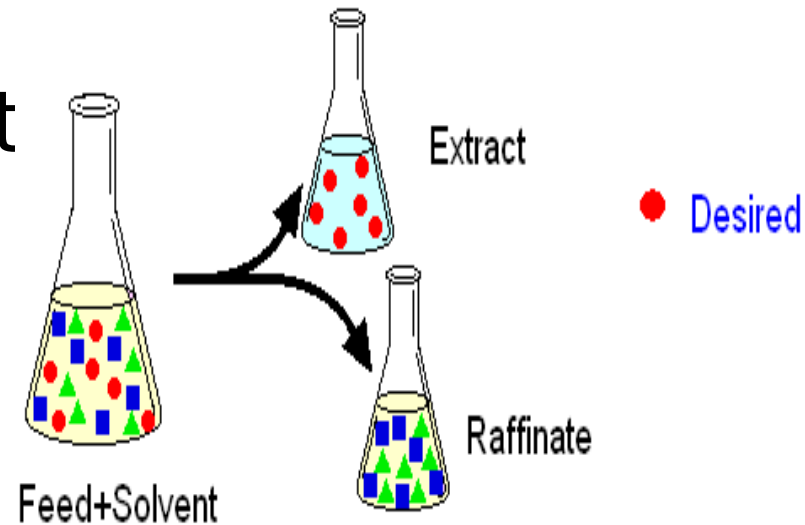
- Powder Charging by PTS.
- Check the material nature, wet, lumps, color or any abnormality.
- These can lead to incomplete reaction or formation of impurities.
- Material should be free flow if material is dry.
- During powder charging stirring shall be on condition.
- After charging material flush the line with suitable solvent and flush with nitrogen if applicable.
- Remove the line and dry the PTS system to avoid the contamination.
- Opening shall be cover with polythene bag.
- Store it designated place.

EXTRACTION

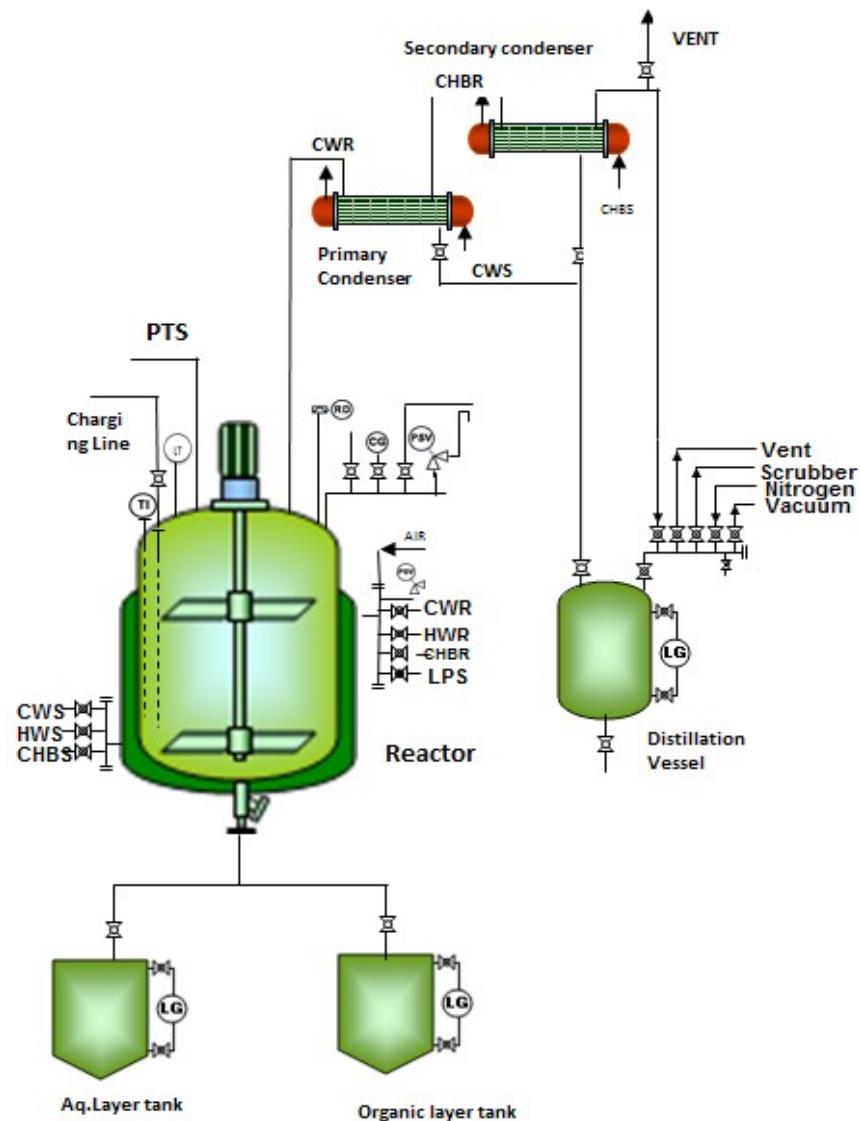
- **Extraction** is a separation process consisting in the separation of a substance from a matrix. It includes Liquid-liquid extraction, and Solid phase extraction.
- Extraction is the withdrawing of a active molecule or waste substance from solid or liquid mixture with suitable solvent.
- The solvent is not or only partial miscible with the solid or liquid. By intensive contact the active agent transfers from the solid or liquid mixture (Raffinate) into the solvent (Extract).
- After mixing the two phases are separate which happens either by Gravity or filtration.

• Factors affecting Extract

- Temperature
- pH
- Agitation & Mixing
- Density
- Temperature



- Normally after the acid base reaction, extraction is carried.
- After extraction both the impurity layer and the product layer are separated by settling the reaction mass.
- Suitable solvent is used for washing the product layer to get the desired product.



Precaution extraction and layer separation

- After reaction if mass is heterogeneous then mass will settle
- Temperature is important if temp is higher then separation is clear.
- If after reaction completion sudden cooling and chilling may lead to turbidity then layer is not clear.
- If cooling or chilling is taken more time then reaction may lead to impurities formation, or emulsion formation due to over stirring and reaction mass becomes sticky.
- Extraction will be always at higher temperature then solubility is better.
- More stirring may lead to emulsion and may lead layer separation to take more time and also density may vary.
- Work up and extraction temperature normally not mentioned in batch production.
- Acid and base extraction is too critical, for acid medium product will be always in organic layer and base medium product will be in aqueous layer and impurities layer shall be separated carefully if layer is not clear and some amount of impurities layer enters into product layer this may impact on quality.

1. What is SCADA and its uses?
 - Supervisory Control And Data Acquisition and can be use for data acquisition and can control operation through system
2. What are safety feature is installed on reactor?
 - Safety Relief Valve
 - Rupture disk
3. What are the reactants or KSM ?
 - Raw material and Key starting material.
4. What is chemical reaction?
 - It is unit process and involved two or more than two chemical react each other to get desired product in specified condition.
5. What is extraction?
 - **Extraction** is a separation process consisting in the separation of a substance from a matrix. It includes Liquid-liquid extraction, and Solid phase extraction.
6. Factors affecting Extractions :
 - Temperature
 - pH
 - Agitation & Mixing
 - Density
 - Temperature

- Abnormalities should be observed and reported
 - Due to brine non availability time of cooling, reaction, work up has taken longer time than previous batches
 - Filtration/centrifugation takes more time than regular batches the hold time increases.
 - During separation, a portion of unwanted layer has gone while transferring

Distillation

- Atmospheric distillation
 - Simple distillation
 - Fractional distillation
- Vacuum Distillation

Evaporation

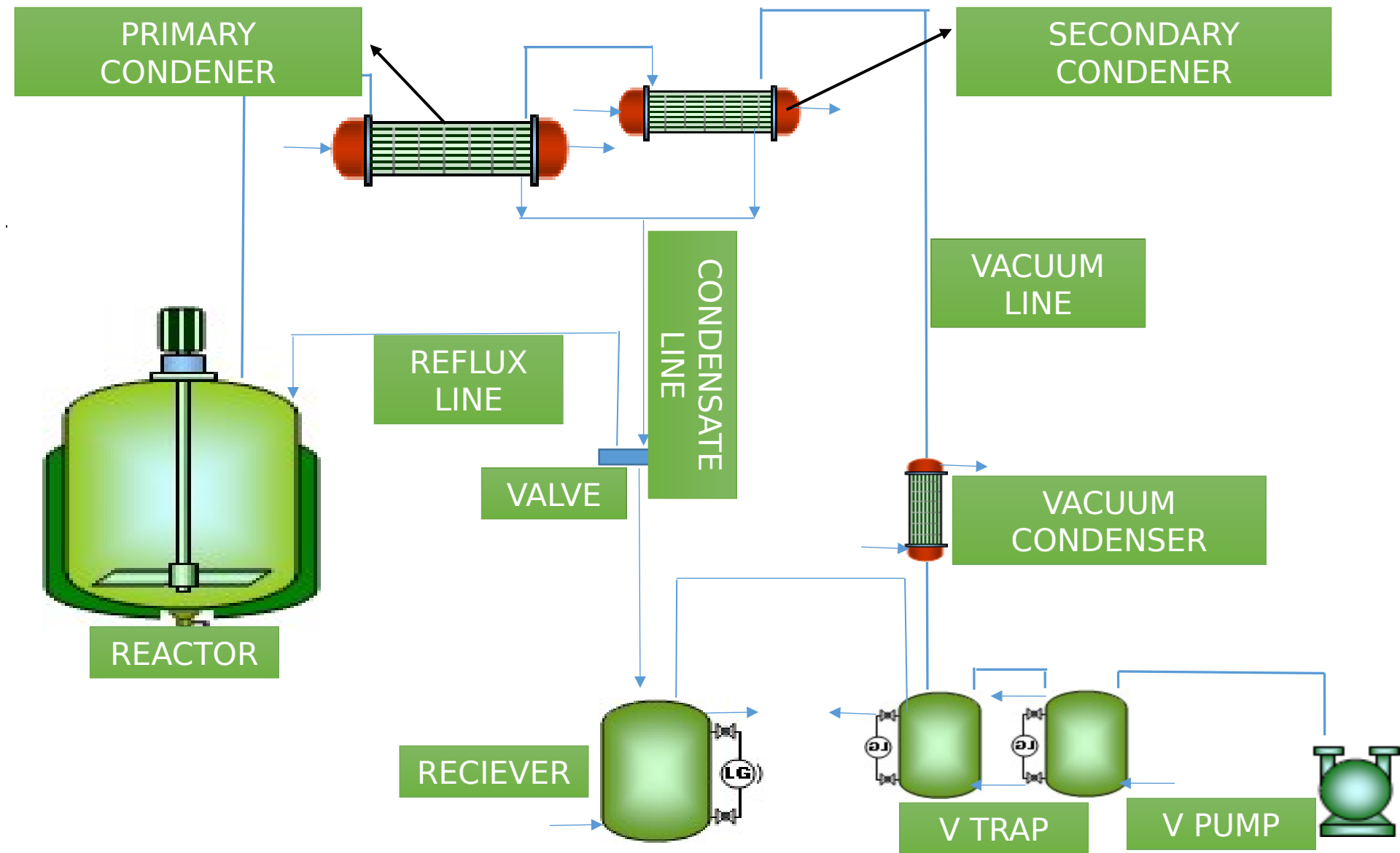
- Rising Film evaporator
- Falling film evaporator
- Agitated thin film evaporator

- **Distillation** is a process of separating the component substances from a liquid mixture by selective evaporation and condensation.
- Distillation may be a partial separation that increases the concentration of selected components of the mixture.
- Distillation is the process exploits differences in the volatility of mixture's components.
- Distillation is a unit operation in API industry for the process
- Distillation is a physical separation process and not a chemical reaction

Types of Distillation

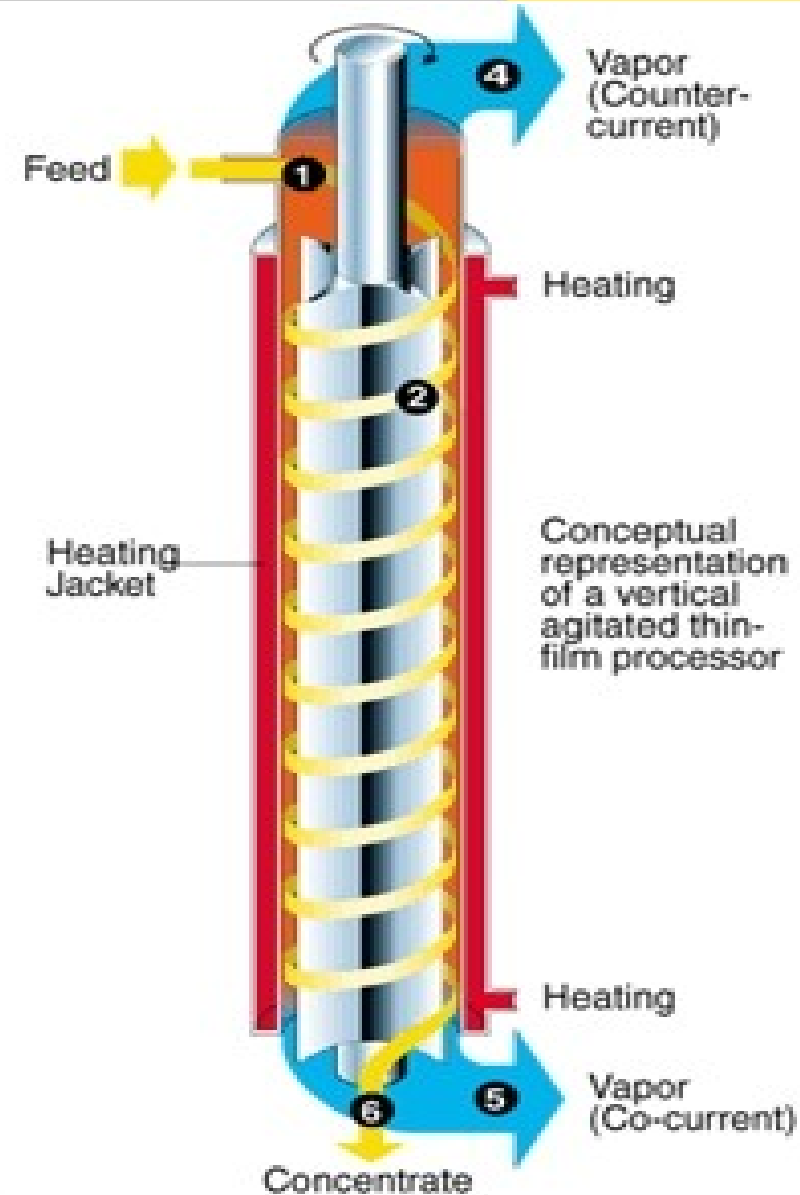
- **Simple Distillation** is the **process** of separating liquid from a solution by boiling and condensing the vapor to obtain liquid..
- **Fractional distillation** is the separation of a liquid mixture into its component parts based on the difference in their boiling point and heating them to a temperature at which one or more fractions of the compound will vaporize.
- **Vacuum distillation** is a method of **distillation** whereby the pressure above the liquid mixture to be distilled is reduced to less than its vapor pressure (usually less than atmospheric pressure) causing evaporation of the most volatile liquid(s) (those with the lowest boiling points).
- In which distillation do we close the condenser vent?
- If steam is used what precaution one should take before start

Vacuum Distillation Setup



Agitated Thin Film Evaporator

- Evaporation is used to concentrate a solution of non volatile solute and a volatile solvent. A portion of the solvent is vaporized to produce concentrated solution
- Feed is introduced tangentially.
- Agitator throws the liquid to the wall, creates a thin film on inside surface of evaporator
- Heat transfer from jacket
- Film flows under gravity and becomes concentrated
- vapors leave from the top to condenser
- Not suitable for highly viscous and sticky materials



1. What is distillation and Type of distillation?
 - Distillation is a process of separating the component substances from a liquid mixture by selective evaporation and condensation.
 - Atmospheric distillation
 - Simple distillation
 - Fractional distillation
 - Vacuum Distillation
2. What is the evaporation and type of evaporators?
 - Evaporation is a type of vaporization of a liquid that occurs from the surface of a liquid into a gaseous phase that is not saturated with the evaporating substance. The other type of vaporization is boiling, which is characterized by bubbles of saturated vapor forming in the liquid phase.
 - Rising Film evaporator
 - Falling film evaporator
 - Agitated thin film evaporator

Principle: Crystallization is based on the principles of solubility. If a saturated hot solution is allowed to cool to super saturation, then the solute is no longer soluble in the solvent and it forms crystals of pure compound.

Crystallization is the (natural or artificial) process of formation of solid crystals precipitating from a super saturated solution..

The crystallization process consists of two major events.

1. Nucleation
2. Crystal Growth

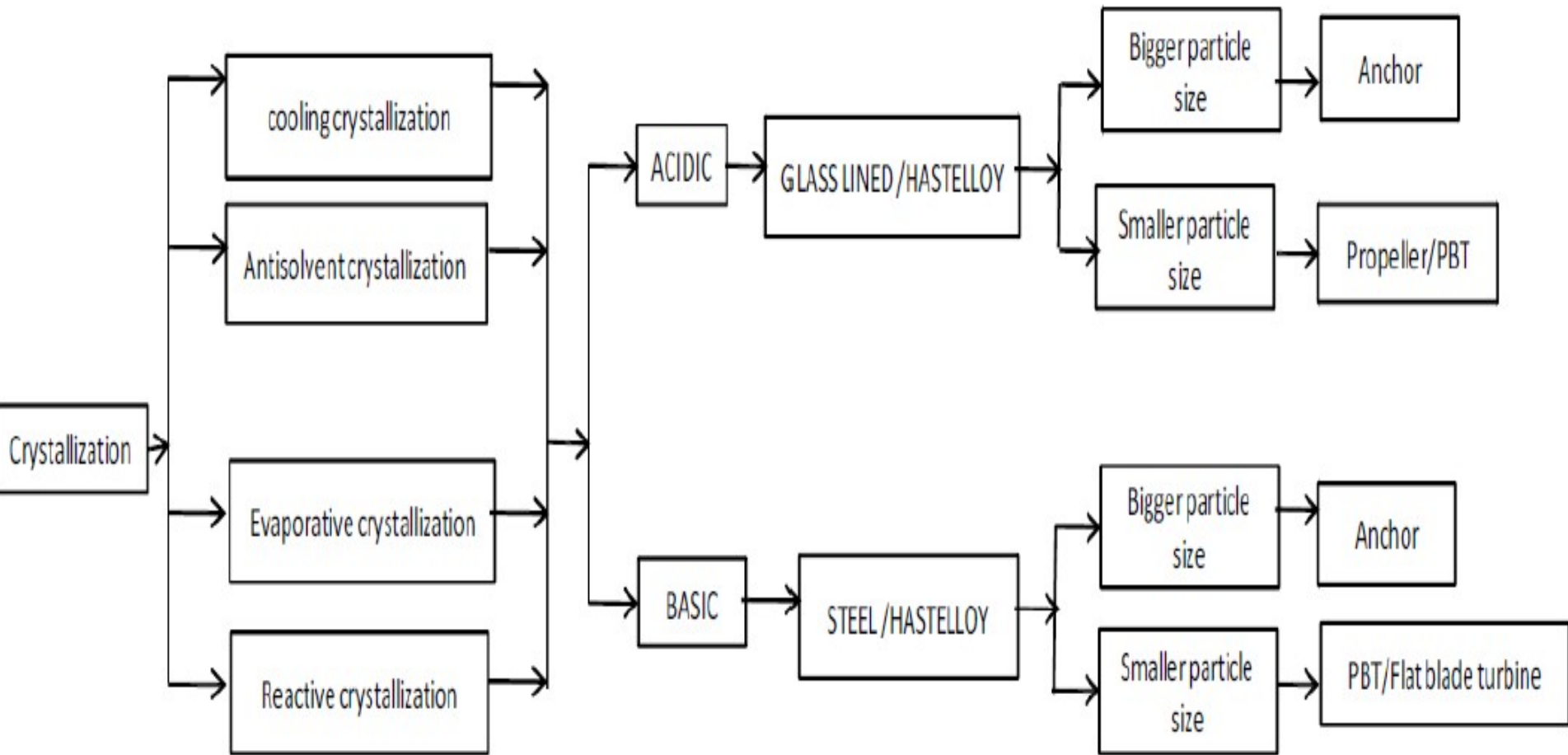
Factors for Crystallization

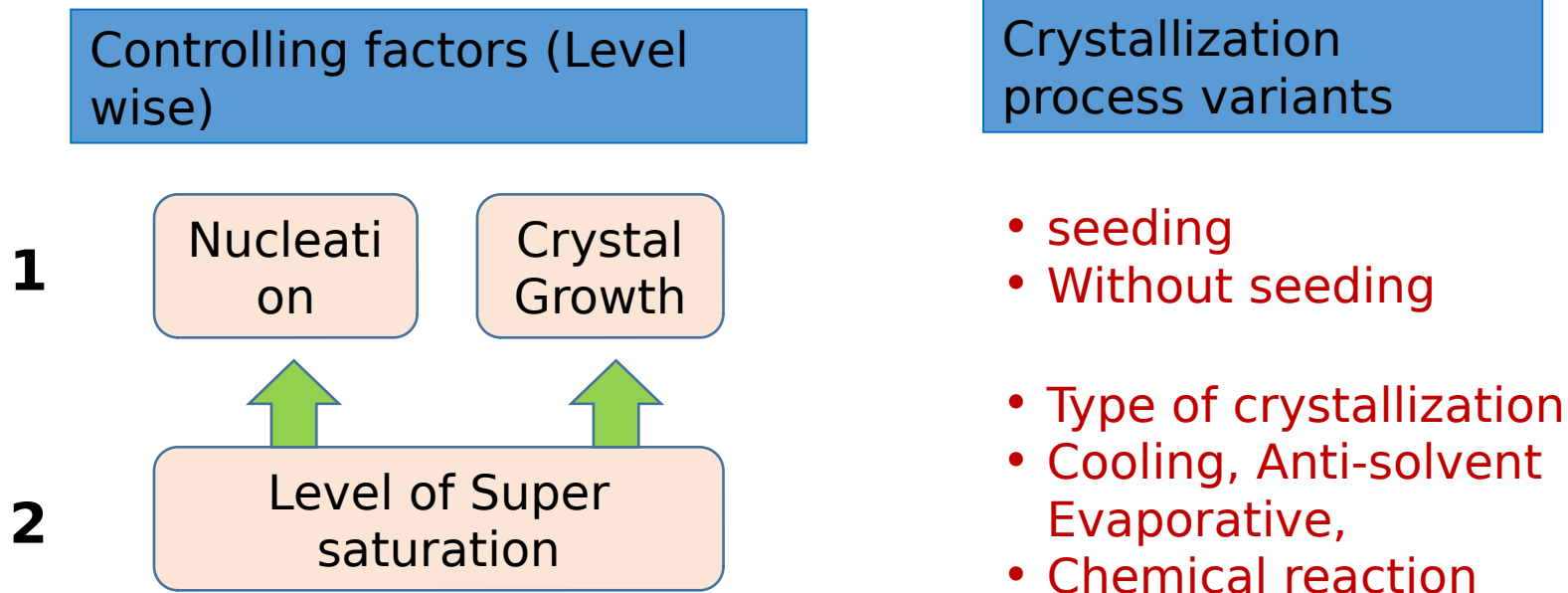
3. Solubility increases with increase in temperature & vice versa
4. Super saturation – when a saturated solution is cooled it become super saturated leading to precipitation

- **Cooling crystallization** - By Temperature change
- **Evaporative crystallization** - By Evaporation of solvent
- **Reactive crystallization** - By Chemical reaction
- **Anti solvent crystallization** - By changing the solvent composition

WIDELY USED METHOD FOR OBTAINING POLYMORPHS IS COOLING AND ANTISOLVENT CRYSTALLIZATION

SELECTION OF REACTOR & AGITATOR FOR CRYSTALLISATION





balance between crystal growth & nucleation is key for PSD in any crystallization

ICH Q6A defines Polymorphs as *drug substances that exist in different crystalline forms differing in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms."*

POLYMORPH PROPERTIES

- Dissolution rate
- Rates of solid state reaction
- Physical/chemical Stability
- Rate of nucleation/crystal growth
- Hygroscopicity
- Compatibility and tableting
- Handling, filtration, flow and blending
- Thermal properties - melting point, heat of reaction (enthalpy)

How is Polymorph form controlled in API manufacture?

- It is important to control POLYMORPH during API synthesis.
- Different polymorphs can have different solubility and can affect recovery of API.
- Purification efficiencies can vary due to differential exclusion of impurities.
- Filtration and transfer characteristics often differ between forms.
- Ease of drying can vary due to different abilities to bind solvent and water in the crystal lattice.

Crystallisation parameters like

- temperature,
- supersaturation level,
- rate of concentration or cooling, and
- seeding

must be controlled to ensure consistency of solid form in API.

Better processing characteristics:

Crystallization technique is used to change the micrometrics of drugs such as compressibility and wet ability.

Improved physical stability:

Crystalline forms play an important role in product properties such as suspension stability and hardness of a tablet.

Ease of handling:

Crystallization facilitates various operations such as transportation and storage.

Better chemical stability:

Crystallization increases the stability of drugs. For example, amorphous penicillin G is less stable than crystalline salt.

Improved bioavailability:

Some drugs are more effective in their crystalline form. For example, Penicillin G does not dissolve immediately in the gastric fluids. Therefore, its degradation decreases. Hence, bioavailability of penicillin G enhances.

Sustained release:

Drug substances with different sizes of crystals can be used in the production of sustained release dosage forms.

Analytical Technique	Description of Method
Single Crystal X-ray Diffraction	provides the most complete information about the solid state. It will give information about the position of molecular groups within the crystal and thus actually defines the differences between the different forms.
Powder X - Ray Diffraction	Crystalline materials in powder form give characteristic X - ray diffraction patterns made up of peaks in certain position and varying intensities.
Differential Scanning Calorimetric (DSC)	It measures the heat loss or gain resulting from physical or chemical changes within a sample
Thermo gravimetric analysis (TGA)	It is a technique that measures changes in weight that occur to a sample as function of temperature over time.

1. What is crystallization and what are the two major process?
 - Crystallization is the (natural or artificial) process of formation of solid crystals precipitating from a super saturated solution..
 - Nucleation
 - Crystal Growth
2. What are the type of Crystallization?
 - Cooling crystallization
 - Evaporative crystallization
 - Reactive crystallization
 - Anti solvent crystallization.
3. What is the Polymorph?
 - Polymorphs as *drug substances that exist in different crystalline forms differing in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.*
4. What are the analytical techniques for analysing the amorphous?
 - Single Crystal X-ray Diffraction
 - Powder X – Ray Diffraction
 - Differential Scanning Calorimetric (DSC)
 - Thermo gravimetric analysis (TGA)

FILTRATION

Separation of solids from fluids

Terms used in filtration

- Feed
- Filter media
- Filtrate
- Wet cake

Filtration working principle

- Filter due to Pressure difference
- Filter due to Centrifugal force

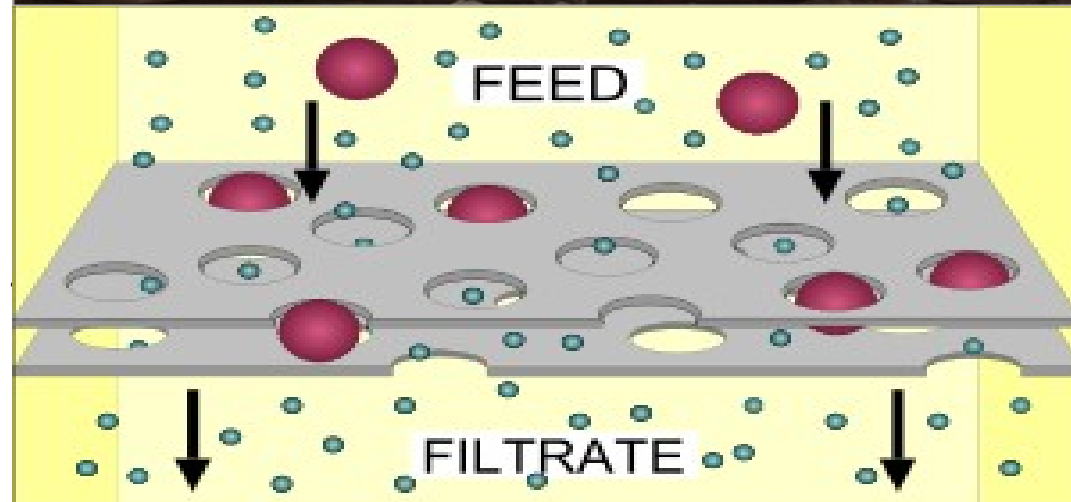
Driving force of filtration are

Gravity

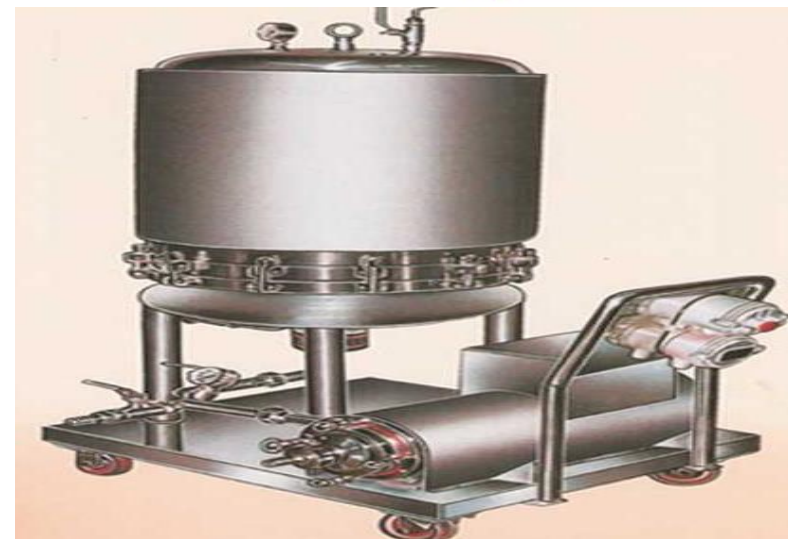
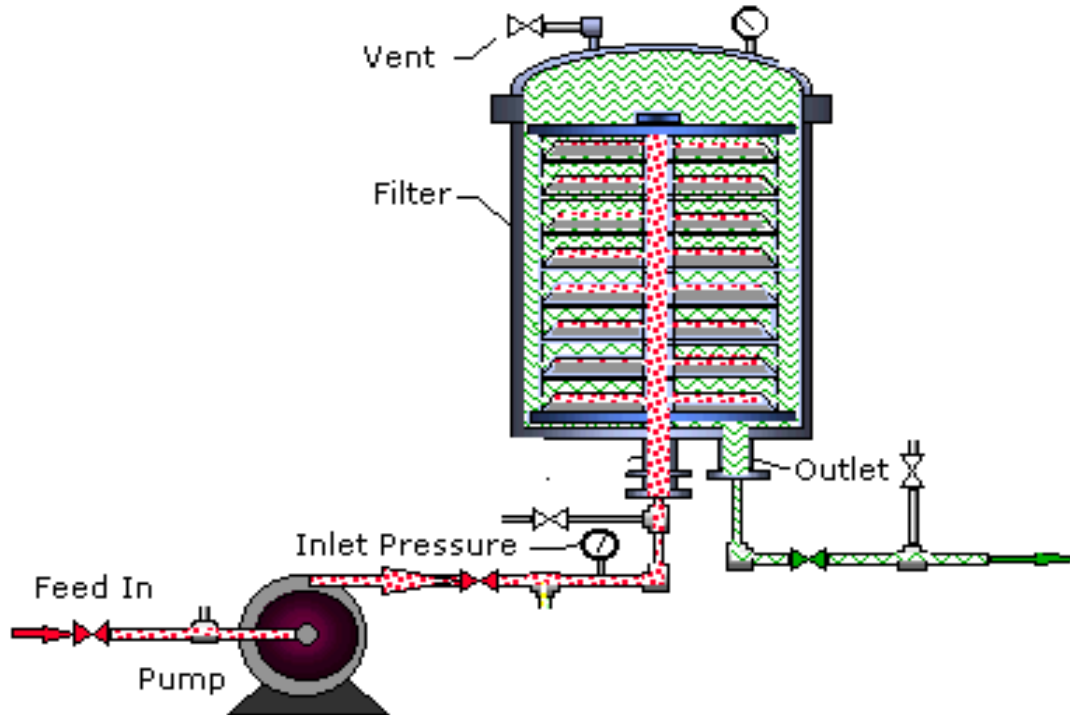
Vacuum

Pressure

centrifugal



SPARKLER FILTER/MICRON FILTER



Factors Affecting Filtration



Filtration Factors	Process Impact
Cake Compressibility	If the cake is rigid and incompressible the rate of filtration is directly proportional to the pressure of filtration and square of the filtration surface. The rate of filtration is inversely proportional to the viscosity of the filtrate The rate of filtration is inversely proportional to thickness of cake. If the cake is extremely soft or compressible, the rate of filtration is independent of pressure of filtration – centrifugal force is to be used.
Effect of Pressure	Increase in Pressure always brings about a nearly proportionate increase in the rate of filtration. However, for cake composed of flocculent or slimy substances, rate of filtration increases only slightly with the increase of pressure.
Cake Thickness	In the early stage of filtration, it has no significant effect on rate of filtration, but as cake is very thin and as the time increases, the thickness of the cake increases and it reduces the rate of filtration.
Effect of Viscosity	The rate of filtration is inversely proportional to the viscosity of filtrate.

FILTRATION EQUIPMENT



Agitated Nutche Filter Drier



Pressure Nutche Filter or
Nutche filter

CENTRIFUGE

- a machine with a rapidly rotating perforated basket that applies centrifugal force to its contents, typically to separate liquids from solids.

• Type of centrifuge.

1. Top Discharge
2. Bag lifting
3. Bottom Discharge
4. Comiconder

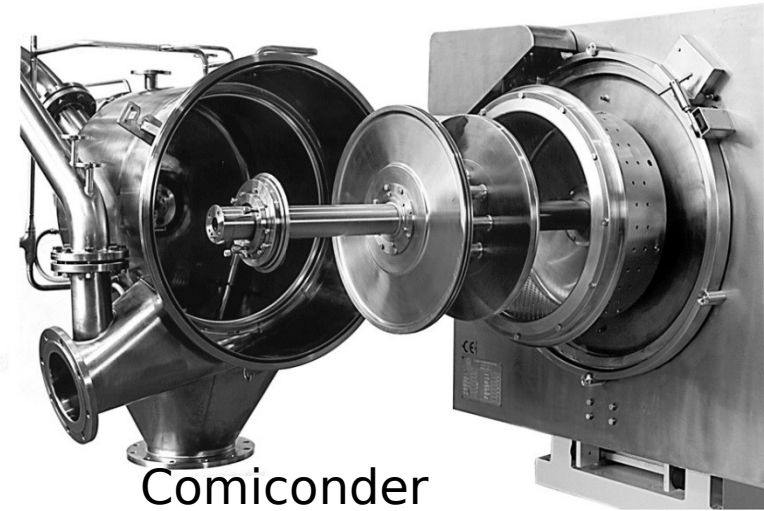
Top discharge



Bag lifting
discharge



Bottom
discharge



Comiconder
discharge

1. What is filtration and what are term used in filtration?
 - Separation of solids from fluids
 - Feed
 - Mother Liquor
 - Filter Media
 - Wet cake
 - Filtrate
2. What are the driving force of filtration?
 - Gravity
 - Pressure
 - Vacuum
 - Centrifugal
3. What are the factor effecting the filtration?
 - Cake Compressibility
 - Effect of Pressure
 - Cake Thickness
 - Effect of Viscosity
 - Effect of Temperature
4. What are the type of Centrifuge?
 - Top Discharge
 - Bag lifting
 - Bottom Discharge
 - Comiconder

Objective:

Removal of solvent by evaporation from a solid, semi-solid or liquid to form the solid material

Purpose

- Improves the flow ability, compressibility, stability.
- Driers commonly used in API industry are:
 - Tray drier
 - Vacuum tray drier
 - Fluidised bed drier
 - Rotary cone vacuums drier
 - Freeze drier/ lyophilized
 - Spray drier – amorphous materials
 - ANFD – all types of products
 - ATFD – where amorphous material is required

AIR TRAY DRIER

Advantages:

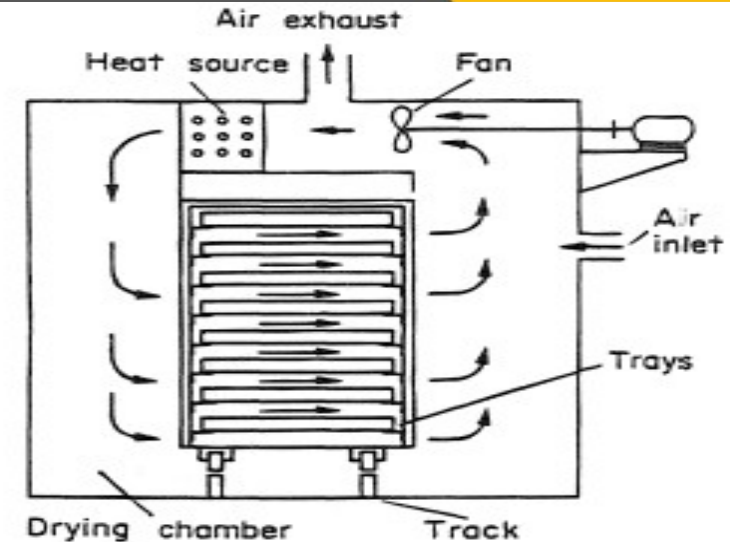
- Handling of material will be easy
- Product changeover can be done effectively by easy cleaning
- Maintenance is easily
- Cheaper compared to other driers

Disadvantages:

- Expensive to operate
- Great heat losses;
- Moisture content varies across the trays within same lot .

• Precautions

- Periodic disturbance during drying to break the hard surface and lumps
- Materials should not have lumps
- Selection of representative sample to check end point



VACCUUM TRAY DRIERS

Advantages:

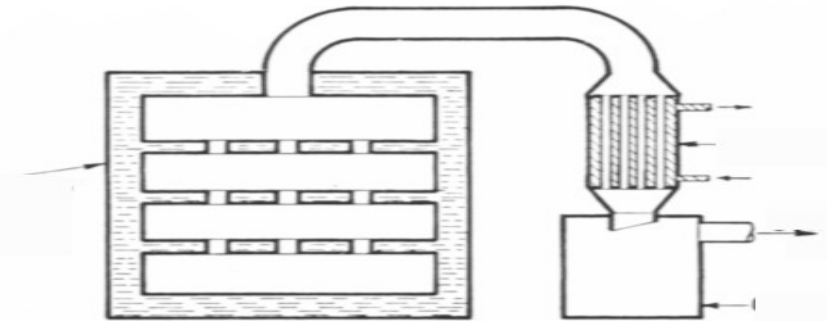
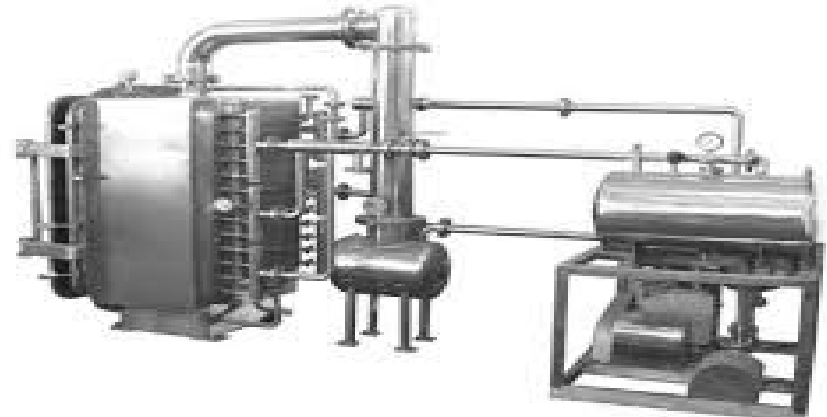
- Handling of the materials is easy
- Large heat transfer surface area.
- Heat sensitive material

Disadvantages:

- Dryer is a batch type process .
- Low efficiency and expensive.
- Cleaning is laborious process
- Maintenance is also difficult

• Precautions

- Start vacuum after getting required temperature
- Periodic disturbance during drying to break hard surface and lumps
- Materials should not have lumps
- Selection of representative sample to check end point



ROTARY CONE VACUUM DRIERS

- The equipment can cause changes to polymorph and suitability should be assessed.
- Dust filter is provided to filter solid particles

Advantages:

- Low drying temperature, fast drying.
- Uniform drying.
- Easy to clean internal surface.

Disadvantages

- Continuous vacuum maintenance during process.

Precautions

- Delumping before putting into RCVD
- Inertisation before start of vacuum
- Frequent nitrogen purging to avoid bag choke
- Bag may fall off if the groove is worn out causing particles
- Particle accumulation in vacuum line which may degrade & cause black particles during or after cleaning



FLUIDISED BED DRIER

Filtered air is blown by blower and heated to required temperature to pass through the bed from the bottom of the perforated bowl. The air escapes from finger bags fitted to the drying chamber while the powder gets arrested.

If air velocity is greater than the settling rate of the powder then the solid bed is fluidized.. If air velocity is too low it will not fluidize. If too high it can lead to fines and entrainments

Due to regular contact of powder with air, material dries.

This airflow is generated by a blower fitted at exhaust of the equipment.

The material sticking to the bag is removed by periodic automatic bag shaking (and the blower is cut off)

Bag chocks or bag damage (integrity) are identified by differential pressure gauge which gives alarm/ switch off if the set point is crossed .



Fluidized Bed
Drier

Advantages:

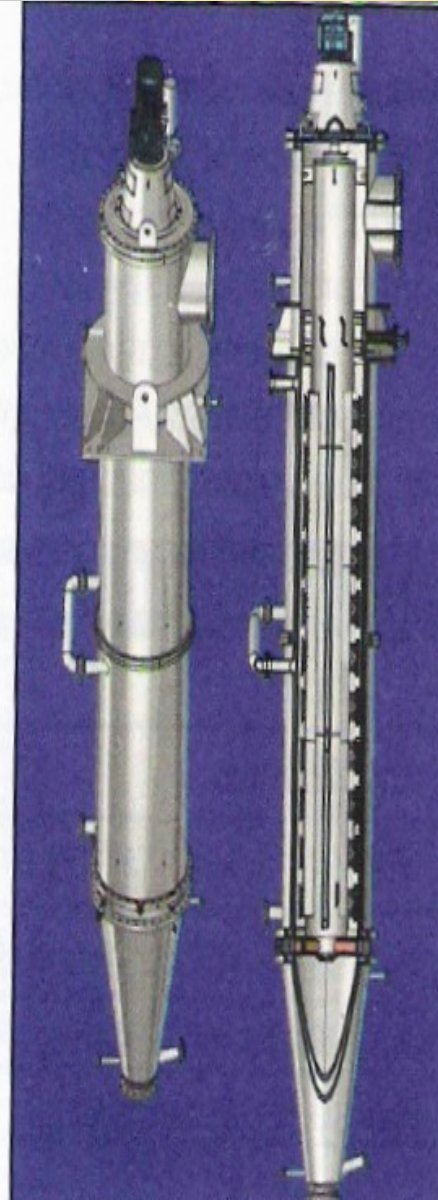
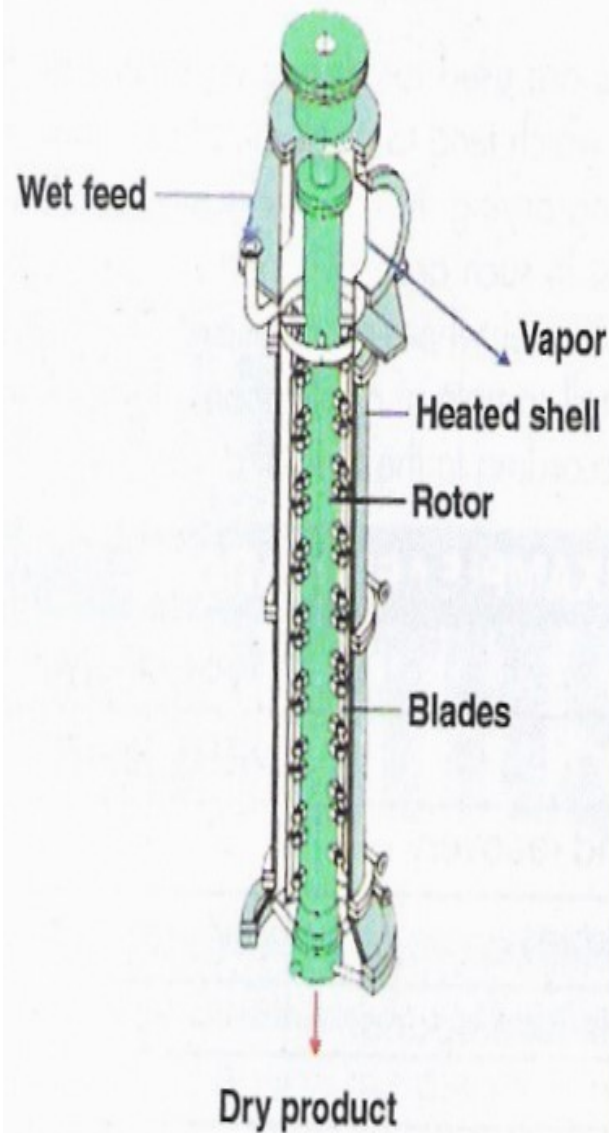
- Efficient heat and mass transfer give high drying rates
- Temperature of a fluidized bed is uniform and can be controlled precisely
- Handling of material will be easy
- Cleaning for product change over will be easy
- High output from a small floor space
- Preferable for water drying products

Disadvantages:

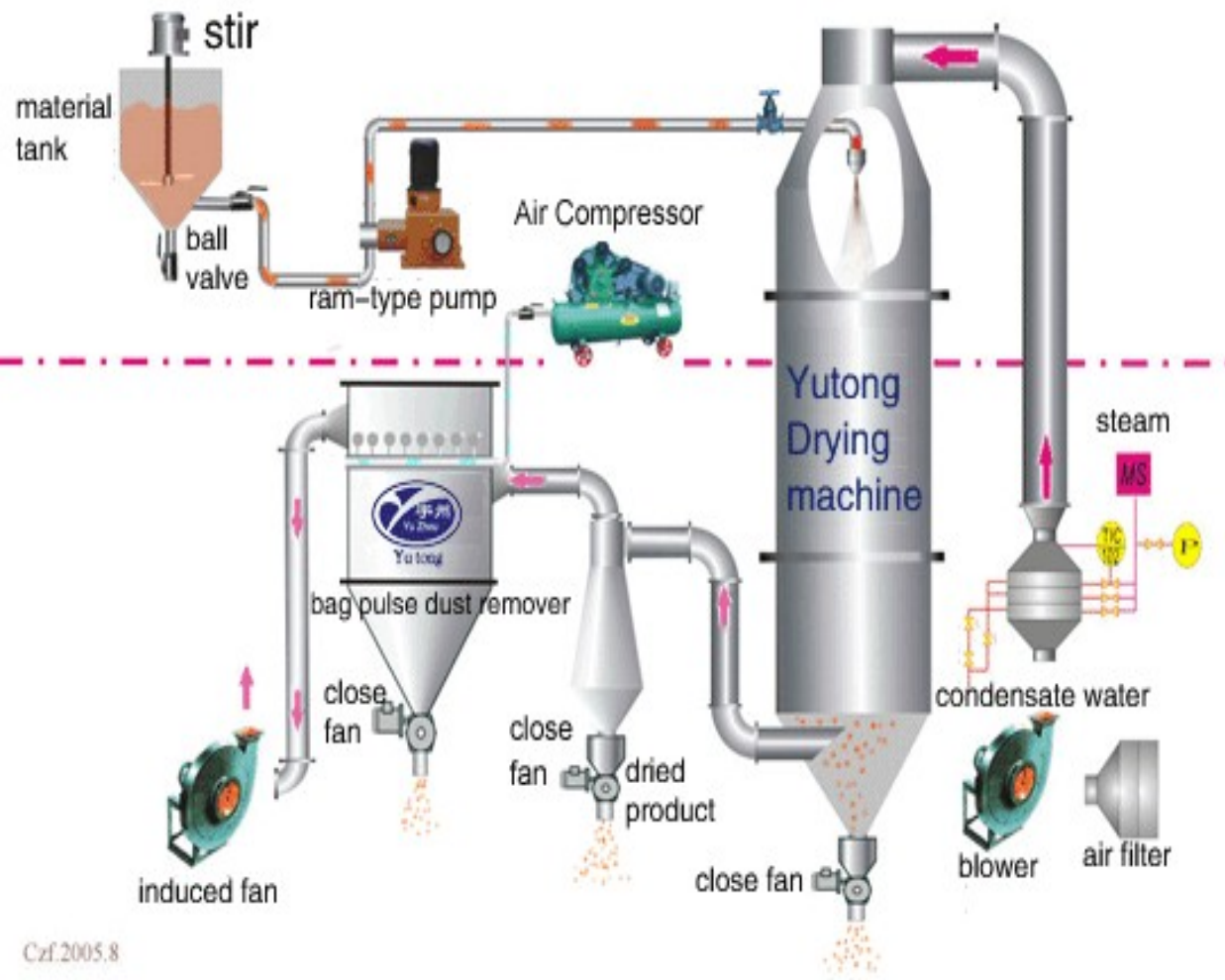
- Many organic powders develop electrostatic charges during drying. To avoid this efficient electrical earthing of the dryer is essential.
- Turbulence of the fluidised state of granules may cause attrition of some materials resulting in the production of fines.

AGITATED THIN FILM DRYING

- **Working:** The feed product is evenly distributed by the rotor and its wipers over the heating surface, forming a thin liquid film of uniform thickness. Highly turbulent swirls are produced at the tip of the rotor blades and wipers with intensive mixing and agitation of the product, as it comes into contact with the heating surface.



SPRAY DRIER



This is for amorphous powders and not for crystallized product
Define atomization
Types of atomization
Controls of droplet size
The liquid mass should be completely solid free
Nozzles can get choked with particles settling on the aperture
Bag pulse dust remover
3 places powder is getting collected

Advantages:

- Drying is very fast
- Heat sensitive material can be dried
- Products will have fine size

Disadvantages:

- Occupy more space if it is in recirculation mode
- Operating cost is more if it is once through

FREEZE DRYING

- Freeze drying is a process used to dry extremely heat - sensitive materials. It allows the drying , without excessive damage.
- **Freeze-drying**—technically known as **lyophilisation**, or **cryodesiccation**—is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase.
- In this process the initial liquid solution or suspension is frozen, the pressure above the frozen state is reduced and the water removed by sublimation.
- Thus a liquid -to-vapour transition takes place, but here



Lyophilization

1. What is objective and purpose of drying?
 - Removal of solvent by evaporation from a solid, semi-solid or slurries liquid to form the solid material Improves the flow ability, compressibility, stability.
2. Which are driers are commonly used in API Industries?
 - Tray drier
 - Vacuum tray drier
 - Fluidised bed drier
 - Rotary cone vacuums drier
 - Freeze drier/ lyophilized
 - Spray drier – amorphous materials
 - ANFD – all types of products
 - ATFD – where amorphous material is required
3. what are the advantage and disadvantage of tray dryer?
 - Handling of material will be easy
 - Product changeover can be done effectively by easy cleaning
 - Maintenance is easily
 - Cheaper compared to other driers
 - Expensive to operate
 - Great heat losses;
 - Moisture content varies across the trays within same lot .

1. What is the use of freeze drying?
 - **Freeze-drying**—technically known as **lyophilisation**, is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase.
 - Extremely heat – sensitive materials.
2. What is the working of Agitated thin film dryer?
 - Working: The feed product is evenly distributed by the rotor and its wipers over the heating surface, forming a thin liquid film of uniform thickness. Highly turbulent swirls are produced at the tip of the rotor blades and wipers with intensive mixing and agitation of the product, as it comes into contact with the heating surface

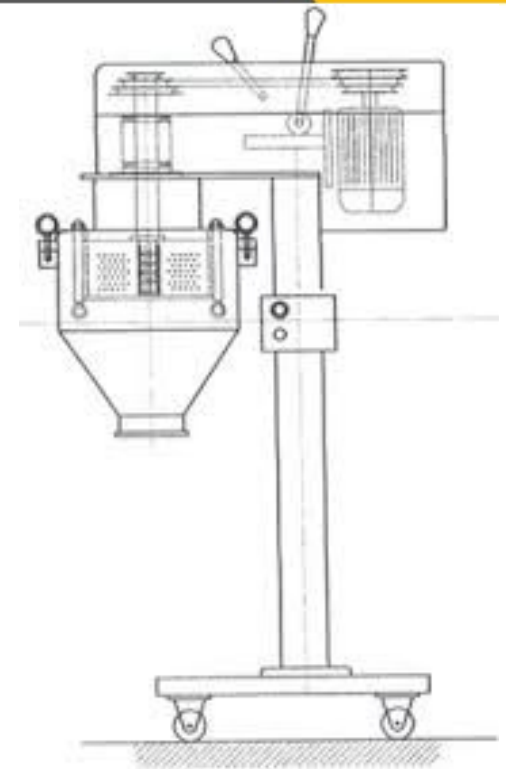
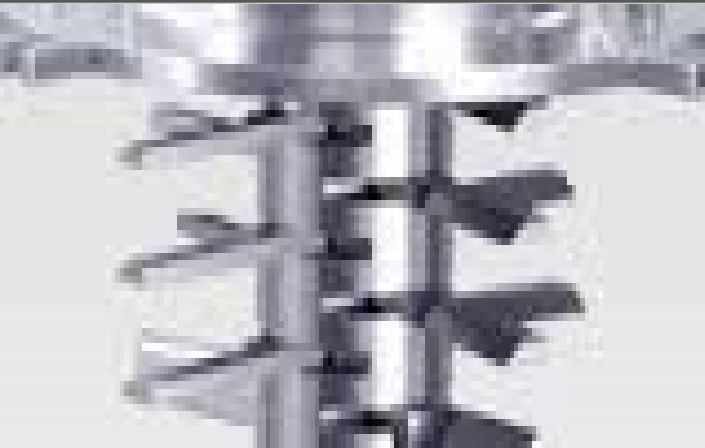
- Particle size reduction
 - Multi-mill
 - Micronizing
- Sifting
- packing

Particle size reduction



- Size reduction is a process of reducing large particles into smaller particles... .
- The most important characteristic governing size reduction is hardness.
- The reason for size reduction increase in surface area per unit volume which helps in
 - better removal of residual solvents
 - better dissolution and disintegration of formulated product

MULTIMILL

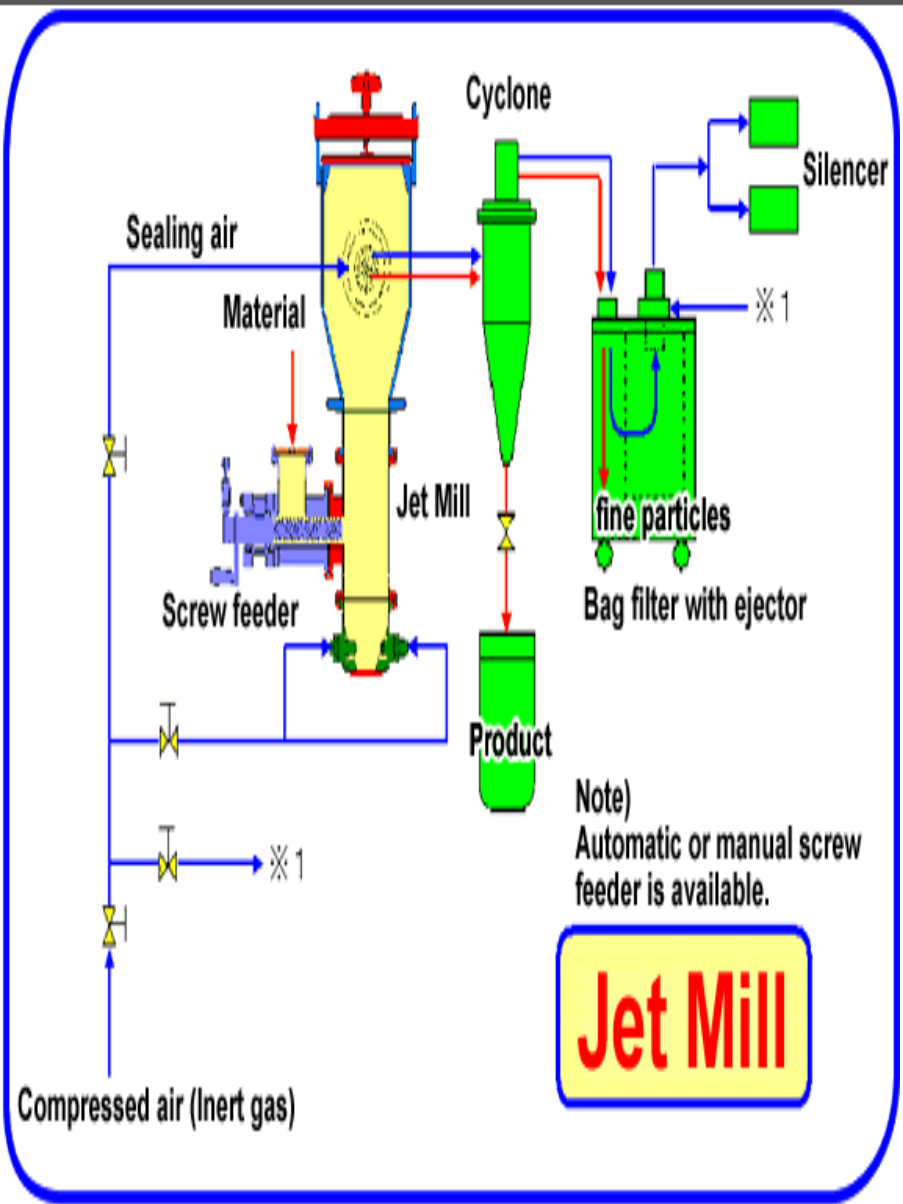


Multimill
assembly

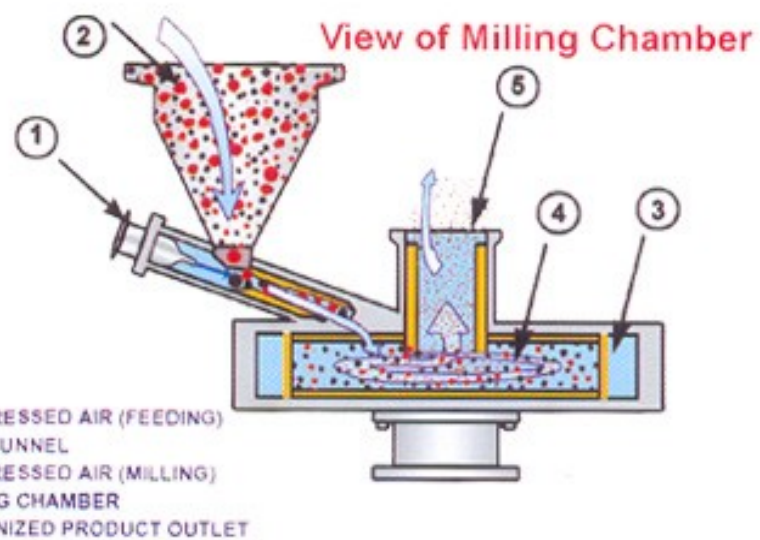


Mesh

Micronizer/ Jet Mill



Jet Mill



Top View



Double Bed Vibro
Sifter



Sifter Sieves



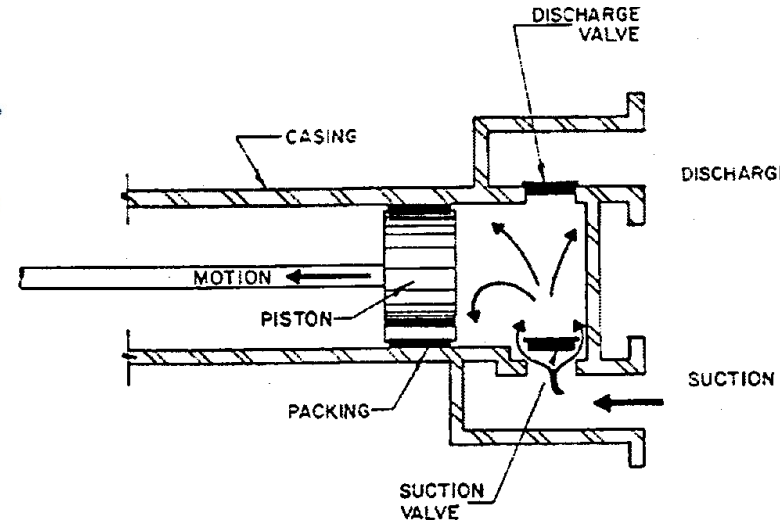
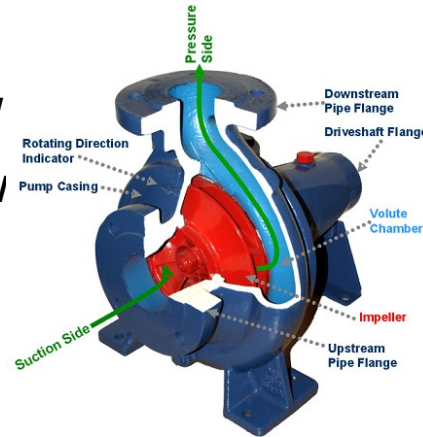
- VNS machine
- Labelling precautions
- How to pack – without leaving any head space
- Checks to be done before packing – bags & drums for extraneous matter

1. What are the flow of material in powder processing?
 - Particle size reduction Multi-mill Micronizing ;Sifting; Packing
2. What is meant by Particle size reduction?
 - Size reduction is a process of reducing large solid unit masses into small unit masses, coarse particles or fine particles. Size reduction process is also termed as Pulverizations.
3. What are the equipment used in particle size reduction?
 - Pulveriser : Pulverisers are used for Grinding different types of materials
 - Micronizer :Operated at high Pressure conditions
 - Sifter :Sifter is used to get Homogeneity of the final material

TRANSFER PUMPS

Centrifugal Pumps

- Very high capacity and low
- Smooth non pulsating Flow



Reciprocating pump

- which includes the piston pump, plunger pump and diaphragm pump.
- It is often used where a relatively small quantity of liquid is to be handled and where delivery pressure is quite large.

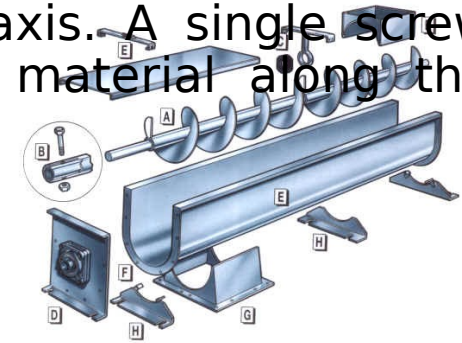
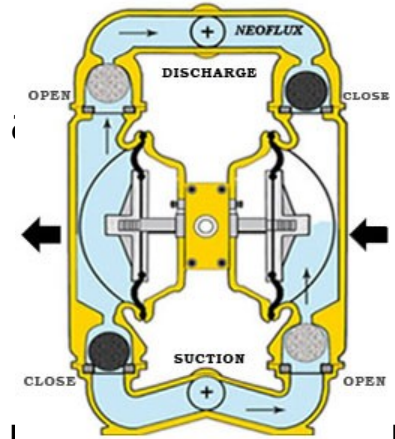
TRANSFER PUMPS

AOD Pump :

- Offer the ability to vary flow and discharge pressure with adjustment of the air supply
- Are able to run dry without damage to pump

Screw pump :

- A screw pump is a positive-displacement (PD) pump that uses screws to move fluids or solids along the screw(s) axis. A single screw rotates in a cylindrical cavity, thereby moving the material along the screw's spindle.



- Different pumps for which types
- pH, temperature, volume, density, solvent nature
- Gasket selection
- Selection

- Vacuum is a region with a gaseous pressure much less than atmospheric pressure.
- Use our terminology to refer to absolute vacuum, high vacuum, low vacuum and atmospheric pressure – mm Hg, kg/cm²

- Water ring pump - Low vacuum to Medium vacuum
- Oil ring pump - Low vacuum to High vacuum
- Dry vacuum pump - High vacuum
- Water jet ejector - Low to Medium vacuum
- Steam jet ejector - Medium to High vacuum
- Water ring pump with steam jet ejector - Medium to High vacuum

Vacuum pumps :

Liquid-ring pump

A liquid-ring pump is a rotating positive-displacement pump.

The most common sealant is water, almost any liquid can be used. The second most common is oil. Since oil has a very low vapour pressure, oil-sealed liquid-ring vacuum pumps are typically air-cooled.



Dry Vacuum Pump

Dry running vacuum pumps are used increasingly throughout industry where there is a growing demand for uncontaminated vacuum, free from oil or service liquid, a requirement for low operating pressures, a flexibility required from batch processes, concern about storage and disposal costs of service liquids and the pressure to minimise life-cycle costs. Moreover sealed unit meets these demands, whilst maintaining a simple, cost-effective solution.



S.No	Valve Type	Process Application	Valve Diagram
1	Ball valve	on/off control without pressure drop, and ideal for quick shut-off - where flow control is not required,	
2	Butterfly valve	flow regulation in large pipe diameters on the utility side	
3	Check valve or non-return valve	allows the fluid to pass in one direction only - mainly on vacuum line, cooling tower to avoid back flow	
4	Diaphragm valve	controls flow by a movement of a diaphragm. For corrosive fluids	
5	Gate valve	mainly for on/off control, with low pressure drop - wherever full opening and closing in utility side	
6	Globe valve	good for regulating flow - reagent addition	
7	Needle valve	accurate flow control - process where drop-wise addition - exothermic reactions	

S. N o	Valve Type	Process Application	Valve Diagram
8	Piston valve	regulating fluids that carry solids in suspension (rarely used in our processes)	
9	Thermal expansion valve	used in refrigeration and air conditioning systems	
10	Pressure Regulating Valve	Gases - Nitrogen/ Air/ NH3/ HCl/H2 Automatically reduces the inlet pressure to a set downstream pressure, regardless of changing flow rate and/or varying inlet pressure.	
11	Control valve	The manual control is replaced by automatic controls through actuator system (based on air regulator).	

- **Heat Transfer**

- The three fundamental modes of heat transfer are conduction, convection and radiation. The rate of heat transfer is dependent on the temperatures of the systems.
- Condensers are heat exchangers that condense vapours coming out from process
- Most commonly used are shell and tube heat exchangers (single pass, multipass).
- Generally shell side vapours, and tube side fluid coolant used (Cooling tower water, Chilled brine, Chilled water)
- Two condensers in series is the typical arrangement for condensation
- Vent is connected to a solvent recovery system where there is final condenser with effective cooling so that nothing is vented to environment

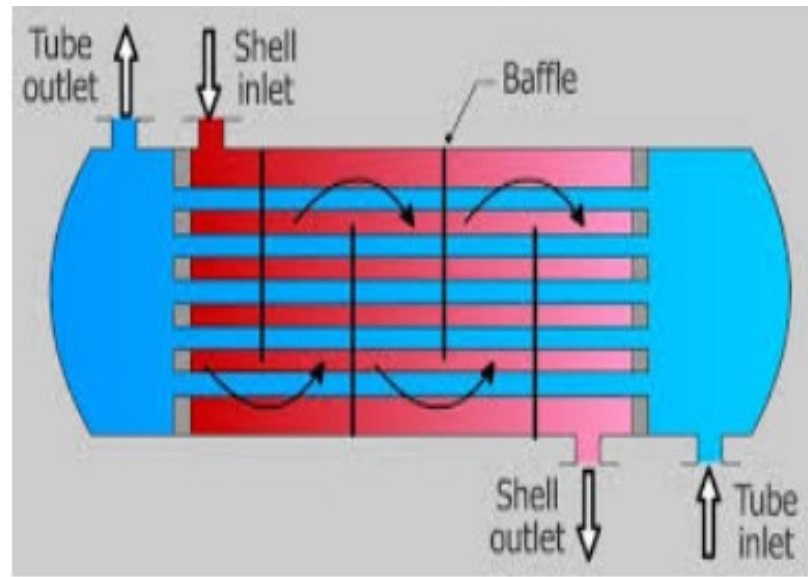
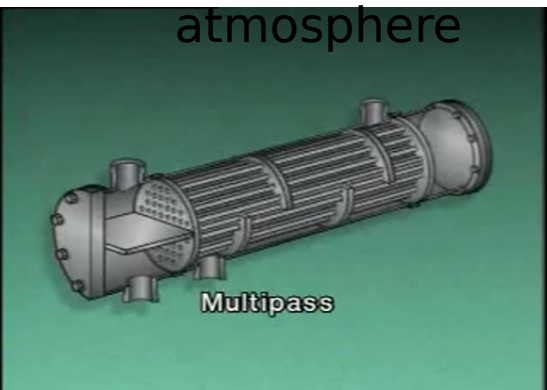
Heat Exchangers

What is the function of Primary & Secondary?

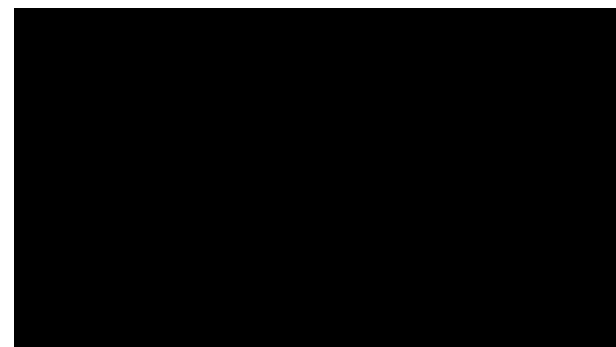
- Primary condensers remove the sensible heat from vapour and CT water is used for the same
- Secondary condensers to remove the latent heat from vapour and Chilled brine / Chilled water is used for the same.

Why condensation is required in the API manufacturing process?

- To recover organic solvents used in the manufacturing process.
- To prevent emission of vapours to atmosphere



Single pass

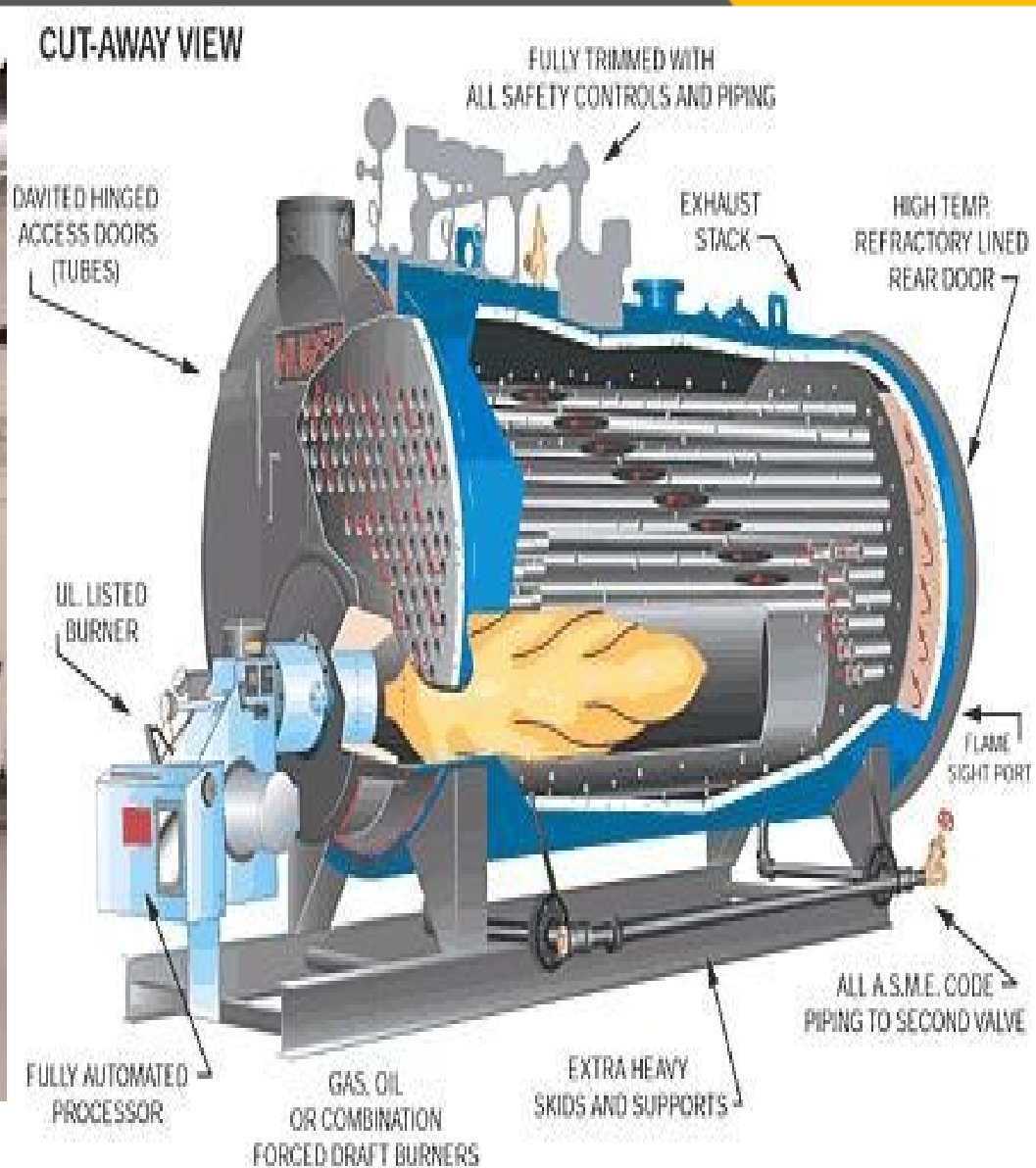


- Boiler
- Cooling Tower
- Chilling Plant
- Purified Water Plant
- Refrigeration
- Scrubber
- Nitrogen Generation
- Air Compressors

BOILER



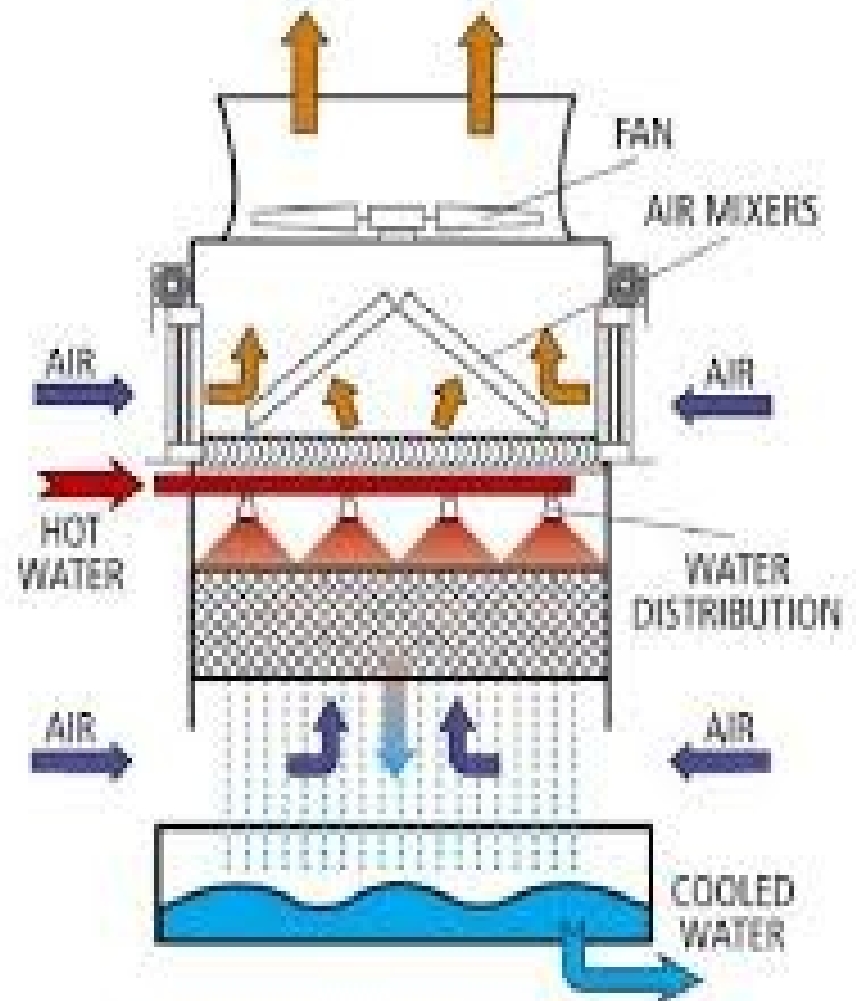
IBR Boiler



COOLING TOWER

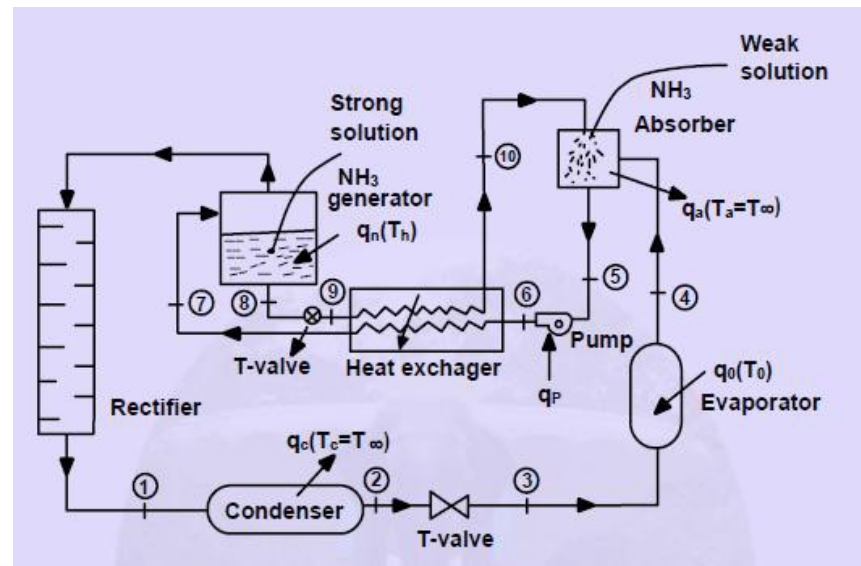
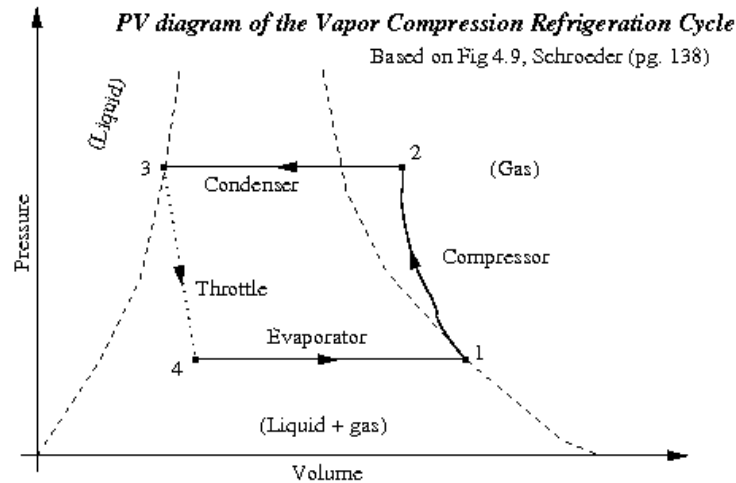
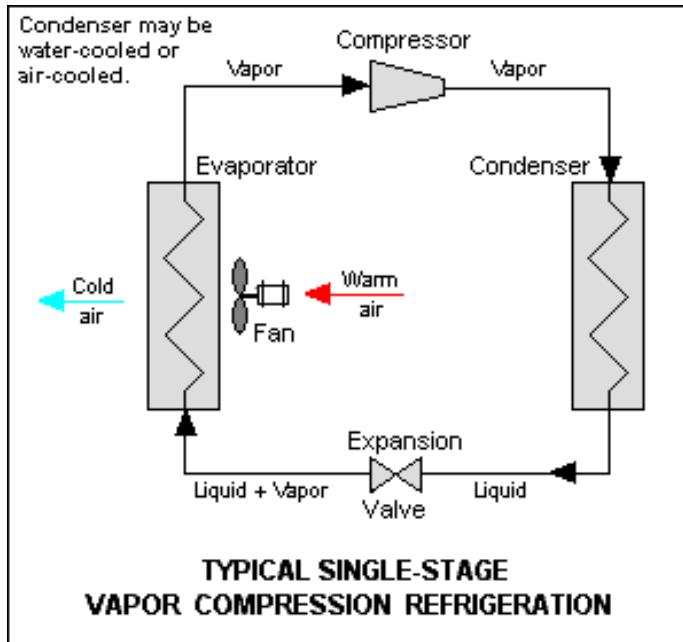


Cooling
Tower



- Cooling tower (CT) water is critical utility for any plant.
- Efficiency of cooling tower and quality of CT water impacts time cycles of cooling operations.
- Blow down: Evaporation and drift losses increase concentration of minerals, hence regular blow down of appropriate quantity is essential.
- Chemicals: Addition of chemicals such as biocide, anti-foam, scale inhibitors to water prevents microbe growth.
- Decrease in CT water temperature results in reduced efficiency of chiller.

VAPOUR ABSORPTION REFRIGERATION SYSTEMS



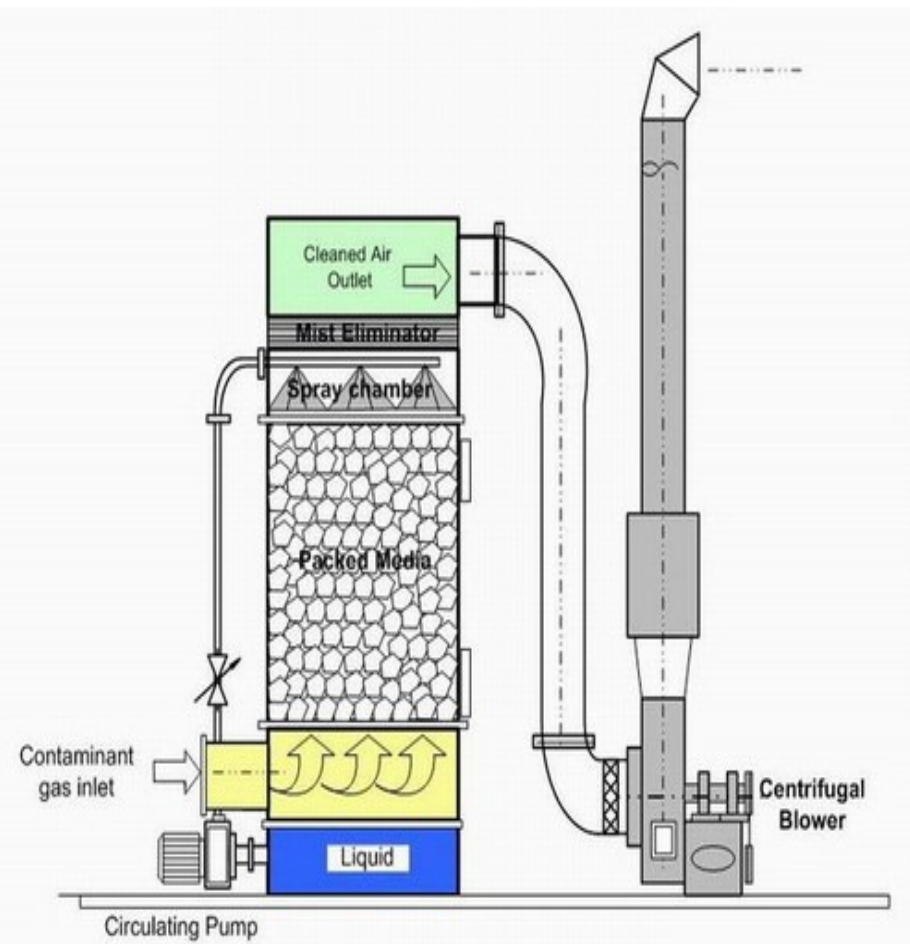
CHILLED BRINE/CHILLED WATER

Brine Chilling Plant are used for producing and maintaining **Chilled Brine** through refrigeration process. **Brine** is a thermal fluid, which is a liquid or a mixture of liquid with plain water, which remains in liquid state even in sub-zero temperatures without freezing.



SCRUBBERS

Air-stream pollution control device which uses liquid spray to remove solid and liquid particulate matter (which washes out) and gaseous pollutants (which are either absorbed or chemically neutralized or chemically inactive).



1. For controlling the highly exothermic reactions, if we use normal jacketted vessel we cannot control the reactor temperature by any means. Even though, we maintain high coolant flow-rates we may not achieve set temperature. How will you control the temperature?

We use internal coil-type cooling system which increases the heat transfer area and it will result in maximum decrease of reactor temperature.

2.what do you do when the use of agitators create the problem of Vortex formation?

Vortices leads to the stagnant regions in the vessel. We opt for baffles to avoid this problem.

3. In a Heat exchanger, why we pass cold fluid to shell side and hot fluid to tube side?

It need not to be always colder fluid in the shell. Sometimes we put the less-corrosive fluid in the shell, or the lower-pressure fluid in the shell, or the less-fouling fluid in the shell. Usually, the tubes are easier to produce for a particular metallurgy and pressure rating than the shell, so we want the fluid that is harder to contain in the tubes. Hot fluids are often harder to contain, and have more risk of depositing scale -- so we often put them in the tubes.

4. What are the differences between unit operation and unit process?

In unit operations the mass and concentration change takes place (between entrance and exit points) by providing energy from an external source and no chemical change takes place. Eg: distillation, evaporation, mixing, etc.

While in case of unit process, processing of reactant in the feed takes place i.e reactants in feed get converted into products (by chemical reaction) with the help of either energy supplied to the system or generated by the system.

5. Why do crystalline particles have better filtration rate as compared with slimy/fine powder?

Generally the large the particle size, the higher the filtration rate in Kg/m²/h and the lower the cake moisture. The slimes or extreme fines in a filter feed slurry affect filtration rates to a vastly greater extent. A particularly difficult slurry is one that contains relatively coarse particles and a number of very fine or slimy particles with little or no intermediate size. Filter aids like diatomaceous earth, perlite, powdered coal, fly-ash or paper pulp may be added to the slurry to increase its filtration rate and cake porosity.

6. How will you improve the filtration rate?

By increasing the pressure drop across cake bed – By raising pressure or vacuum. The applied vacuum/pressure creates the pressure differential which is the driving force for filtration and dewatering. High vacuums give somewhat higher rates and lower moistures in all cases except for unusually incompressible cakes.

Viscosity of liquor and temperature - Viscosity is closely related to temperature. As temperature is increased, viscosity is decreased resulting in a higher filter capacity and lower cake moisture. At the same time, increased vapor pressure will help reduce moisture.

Filter medium – Permeability and porosity are prime qualities in cloth selection

Slurry pH - Since slurry pH and particle dispersion are closely related, changes in pH could be one of the most effective methods to improve filterability, if the process can tolerate it.

7. Why cannot we handle hydrogenation reaction in conventional batch reactors?

Rate of reaction in conventional batch reactor is slow as compared with gas induction type vessel. Hydrogenator generates huge amount of Gas-Liquid interfacial area resulting in fastest possible reaction time with comparatively lower catalyst loadings. Where as in Conventional Agitated Vessels Interfacial area is very poor as the agitator is designed only for stirring the mass. Extra catalyst quantity is required to improve sluggish rate of reaction.

8. Exothermic reactions are releasing huge amount of heat during reaction. This heat is continuously removed by circulating sufficient cooling medium to the jacket. What all are control measures to be adopted in case of cooling circulation system fails to bring the reaction mass in safer mode?

- Stop the reactant addition immediately.
- Agitator shall be stopped.
- Quench with suitable pre cooled solvent.
- Start secondary cooling system if provided.

10. How will you detect leakages in the vacuum systems?

The simplest method to find out the leak points in the system is pressure test. Check the working pressure of the particular equipment and apply the pressure to the equipment. Prepare some soap solution and spray over all the flange joints. If leak is there, bubbles shall be observed. Replace the gasket and repeat activity till constant pressure attained in the system.

11. Entire reaction mass charged in to the ANFD and during filtration material passage observed WHAT SHOULD BE DONE.

Immediately close the ML collection valve and reduce the pressure inside the ANFD. If still material passage observed collect the MLS in separate cleaned mobile vessels or anti static container for reprocess. Unload the material and check the integrity of the mesh/ cloth. Replace the cloth and proceed further. Hence it is advisable to check the mesh/cloth integrity and fixing before starting the filtration. It is also preferable to charge the reaction mass lot wise in ANFD instead of charging entire reaction mass at a time.

12. What all are the precautions to be taken to handle the low MIE/OEL value chemicals?

- Ensure proper earthing, bonding and grounding.
- Giving relaxation time while handling/each operation
- Maintain sufficient time duration during charging the materials
- Ensure continuous inertization during material charging

13. During break down of the existing reactor, what are all the parameters need to be checked for transferring reaction mass from existing reactor to new reactor?

- Material of construction (MOC)
- Minimum stirring volume
- Minimum sensing volume.
- Occupancy.
- Agitator type

14. Why spray dryer is preferred over conventional dryers for drying heat sensitive materials?

- The surface area produced by atomization of the liquid feed enables a short gas residence time, ranging from 3-40 seconds depending upon the application, which permits spray drying without thermal degradation.

15. Why air leakages needs to arrest in distillation setup during vacuum distillation and how will improve the solvent recovery %?

- Leakage in the system during vacuum distillation will affect the dew point temperature of the solvent .If dew point temperature of the solvent is low we need to provide utility less than the dew point temperature to collect the distilled solvents

16. Why dip pipe is required in the reactor for charging the solvents?

- To avoid and minimize the static dissipation

17. How the performance of the Scrubber can be measured?

- Draft in the scrubber should be maintained as per design and it can be measured with Manometer mm/wc.

18. What are all the steps to be followed before starting vacuum drying?

1. Vacuum trap to be emptied.
2. Vacuum pump should be started and check whether designed vacuum is achieved in shut off condition
3. Ensure that ΔP across the inlet and outlet of the condenser is NMT 0.3 kg/cm².
4. Ensure that the utility circulation to the condenser and the vacuum trap is continuous and if required release air lock.
5. Leakage test to be carried out in drier is NMT 10 mm/wc.

19. In ANFD operations, prior to drying operation, why is it important to ensure that cake has no cracks? What are the control measures?

Ans: in ANFD, when majority of the filtrate passes through the filter, it indicates the completion of the filtration operation. Prolonged squeezing of the wet cake to expel the filtrate causes development of cracks. The next operation in the sequence is drying of wet cake. If cracks are not sealed before start of drying, then Nitrogen or vacuum used for drying would by-pass through cracks. This will result in trapping of residual solvent and consequent high loss on drying (LOD).

To avoid the above situation, before start of drying it is important to ensure that wet cake has no cracks. If cracks are observed, then those should be sealed by systematic smoothing of cake by lowering agitator blades. This can be easier to do BEFORE drying than during drying operation.

20. What is the need of Blowdown from cooling tower? How it can affect cooling time in process?

Ans: Evaporation of water from cooling tower results in the concentration of minerals present in the water. The minerals content above a certain level will form hard scales and deposition throughout the system. Thus, flushing a portion of high mineral concentration down the drain is required. This process is called Blow down. There is a need to make up for drained quantity by using fresh water.

Scale deposition, in the absence of blow down, can restrict the flow of cooling water to the reactor jacket. In addition, scale formation can take place in the supply header as well as reactor jacket itself. All these probabilities will result in lesser supply of water than required to handle process heat load. This can result in longer time to for cooling during the process.

21. What is the purpose of having 2 condensers in series for most of the reactors in which distillation operation is carried out?

- Ans: As the products & solvent handled in the reactors change, the heat transfer requirements for condensation also change. It is not possible to provide the exact area based on respective solvent. Hence instead of one giant condenser, practice of using two condensers is common to have flexibility.
- In general vapours from reactor contain non-condensable component which has tendency to carry condensable solvent vapours along with it. Therefore, primary condenser having higher heat transfer area is used to condense majority of vapour, using cooling tower water. The vapours escaping from vent of primary condenser are condensed in secondary, using chilled brine or chilled water as utility.

22. In Which case the use of tray dryer is restricted?

- Ans: In API manufacturing, the use of tray dryer is most common for drying the material. However, in case where material has tendency to form lumps, use of tray dryer is restricted. In tray dryer, the air gets heated using steam/hot water and is circulated in direct contact with the material. In cases where the material is sensitive to direct contact with air, Roto cone vacuum dryer instead of tray dryer is used. In case of RCVD, direct contact between heating media and material is avoided.

23. Sticking of mass to the walls of the reactor during Distillation?

- Ans: During Distillation it is commonly observed that the mass is thrown to the walls of the reactor due to the action of agitator. The mass remains stucked to the walls of reactor due to poor heat transfer in the jacket of reactor.

24. What will happen if filter cloth not fixed properly in centrifuge ,hutch filter or ANFD ?

- Ans: If the filter cloth is not fixed properly ,product will carry along with mother liquor which will result in yes yield and the impurity will not washed out properly which will affect the quality of the product.

*Thank
You*

